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THE CHEMISTRY OF
ORGANIC CYANOGEN COMPOUNDS

by

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American Chemical Society
Monograph Series

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General Introduction

AMERICAN CHEMICAL SOCIETY SERIES OF CHEMICAL MONOGRAPHS

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic monographs on chemical subjects. At the same time it was agreed that the National Research Council, in cooperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, secretary of the society, Washington, D. C.; the late John E. Teeple, then treasurer of the Society, New York; and the late Professor Gellert Alleman of Swarthmore College. The Trustees arranged for the publication of the A.C.S. series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company, Inc. (Reinhold Publishing Corporation, successors) of New York.

The Council of the American Chemical Society, acting through its Committee on National Policy, appointed editors (the present list of whom appears at the close of this introduction) to select authors of competent authority in their respective fields and to consider critically the manuscripts submitted.

The first monograph of the series appeared in 1921. After twenty-three years of experience certain modifications of general policy are indicated. In the beginning there still remained from the preceding five decades a distinct though arbitrary differentiation between so-called "pure science" publications and technologic or applied science literature. This differentiation is fast becoming nebulous. Research in private enterprise has grown apace and not a little of it is pursued on the frontiers of knowledge. Furthermore, most workers in the sciences are coming to see the artificiality of the separation. The methods of both groups of workers are the same. They employ the same instrumentalities, and now frankly recognize that their objectives are common, namely the search for new knowledge for the service of man. The officers of the Society therefore have combined the two editorial Boards in a single Board of twelve representative members.

Also in the beginning of the series, it seemed expedient to construe rather broadly the definition of a monograph. Needs of workers had to be recognized. Consequently among the first one hundred monographs appeared works of the form of treatises covering in some instances rather broad areas. Because such necessary works do not now want for publishers, it is considered advisable to hew more strictly to the line of the monograph character which means more complete and critical treatment of relatively restricted areas, and where a broader field needs coverage, to subdivide it into logical sub-areas. The prodigious expansion of new knowledge makes such a change expedient.

These monographs are intended to serve two principal purposes: first, to make available to chemists a thorough treatment of a selected area in form usable by persons working in more or less unrelated fields to the end that they may correlate their own work with a larger area of physical science discipline; second, to stimulate further research in the specific field treated. To implement this purpose the authors of monographs are expected to give extended references to the literature. Where the literature is of such volume that a complete bibliography is impracticable, the authors are expected to append a list of references critically selected on the basis of their relative importance and significance.

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Preface

While associated with an industrial organization manufacturing basic cyanogen chemicals and interested in all possible industrial developments in the field of organic cyanogen compounds, the author had been engaged for a considerable time in making a survey of the chemistry of these compounds. As the volume of information collected assumed large proportions, it seemed desirable to publish the material.

The work is concerned primarily with the *chemistry* of cyanogen compounds and matters such as details of methods of preparation have been dealt with, in general, incidentally to the main theme. Historic matter has been excluded and detailed discussions of various special phases of the chemistry of cyanogen compounds have been avoided. Cyanogen compounds have formed the basis of numerous important syntheses that might reasonably be considered to fall within the scope of the present volume. The inclusion of descriptions of such syntheses would have contributed little, however, to a proper understanding of fundamentals of the chemistry of cyanogen compounds, and would have added greatly to the size of the work. It was deemed sufficient to point out the primary products of transformation of the cyanogen compounds and the more important steps utilized in these syntheses. Within these limitations a determined effort was made to cover the subject in a *comprehensive* manner.

The adopted arrangement in sections appeared to be the natural one into which the available material divided itself. As for nomenclature, the terminology originated by the authors has been adhered to as far as possible. Where changes have been made, these have been in compliance with the conventions generally adopted in the United States.

The author wishes to extend his sincere thanks to Dr. L. J. Christmann for his very material aid toward the publication of this volume; to Messrs. D. W. Jayne, Jr., and R. V. Heuser, and to Dr. R. B. Booth who were kind enough to read the manuscript.

VARTKES MIGRDICHIAN

Greenwich, Connecticut
March, 1947

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THE CHEMISTRY OF
ORGANIC CYANOGEN COMPOUNDS

Chapter 1

Nitriles, Their Formation and Properties

Nitriles, or organic cyanides, contain as a characteristic group the cyano-radical, $—C\equiv N$, consisting of a carbon atom combined to a nitrogen atom with a triple bond. Nitriles are the nitrogen analogs of carboxylic acids in the sense that the three valencies of the carbon atom are satisfied with those of the electronegative nitrogen atom in the same way that the valencies of the carbon atom in a carboxyl radical are satisfied with valencies of the electronegative oxygen and the hydroxyl group. The relationship between the two groups is based on more than merely this similarity, as is indicated by the fact that it is possible, in general, to convert the nitrile group to a carboxyl group, and vice versa, by relatively simple treatments. The cyano-group has a strong electronegative character, and in many respects is similar in its behavior to a halogen atom.

Nitriles are readily obtained by a variety of reactions, and because of their accessibility and the reactivity of the cyano-group which makes possible its transformation into other groups, they have played a very important role in organic synthesis. The principal transformations which nitriles, $R.CN$, may undergo are the following:

(1) Hydrolysis to a carboxylic acid, $RCOOH$.

(2) Partial hydrolysis to an amide, $R.CONH_2$.

(3) Aminolysis leading to the formation of an amidine, $RC(:NH)NH_2$, or an amidoxime, $RC(:NOH)NH_2$.

(4) Reaction with an alcohol, $R'OH$, in presence of a mineral acid resulting in the formation of iminoether, $RC(:NH)OR'$; and simultaneous reaction with an alcohol and water resulting in the formation of an ester, $RCOOR'$.

(5) Reduction to amines, RCH_2NH_2, or $(RCH_2)_2NH$.

(6) Condensation with aromatic compounds, $R'H$, to ketimines, $R'.C(NH).R$; or in the case of hydrocyanic acid to aldimines, $R'.C(NH)H$, which on hydrolysis form aromatic ketones, $R'COR$, or aldehydes, $R'CHO$.

(7) Reaction with Grignard reagents, $R'MgX$, leading to the formation of imino compounds, $RC(NMgX)R'$, which on hydrolysis form ketones, $RCOR'$.

Modes of Formation of Nitriles

The dehydration of carboxylic acid amides or ammonium salts is one of the most general methods of formation of nitriles. In many instances this is the only method available for preparing the desired nitrile. A great many nitriles have been prepared by this method. Dehydration is usually accomplished by means of phosphorus pentoxide:

$$3RCONH_2 + P_2O_5 \rightarrow 3RCN + 2H_3PO_4$$

In some cases phosphorus pentachloride is used as the dehydrating agent. In special cases dehydration can be accomplished by pyrolysis, in the presence of a catalyst.

Nitriles are also obtained by the dehydration of aldoximes usually by means of acetic anhydride. Thionyl chloride and other dehydrating agents have also been used successfully:

$$\mathrm{RCH{:}NOH + (CH_3CO)_2O \rightarrow RCN + 2CH_3COOH}$$

Other methods of formation of nitriles are the following:

Desulfurization of isothiocyanates with metallic copper at 180 to 200°:

$$\mathrm{RNCS + Cu \rightarrow RCN + CuS}$$

Reaction of lead thiocyanate with carboxylic acids:

$$\mathrm{RCOOH + Pb(SCN)_2 \rightarrow RCOOPbSCN \rightarrow RCN + PbS + CO_2}$$

This reaction is applicable in general to aromatic acids. The zinc salt of the acid may be used instead of the acid. The reaction of acids and potassium thiocyanate leading to formation of nitriles is similar and may be included in this class.

Reaction of alkyldichloramines with alkalies:

$$\mathrm{RCH_2NCl_2 + 2KOH \rightarrow RC{\equiv}N + 2KCl + 2H_2O}$$

The reaction of alkaline bromine solution with acid amides leading to the formation of an amine with one carbon atom less than the amide, and the subsequent bromination of the amine formed and its final conversion to a nitrile by excess caustic may be included under this heading.

Reaction of phospham with carboxylic acids:

$$\mathrm{2RCOOH + PN_2H \rightarrow 2RCN + H_3PO_4}$$

Reaction of Grignard reagents with cyanogen:

$$\mathrm{(CN)_2 + RMgX \rightarrow CN.C(NMgX).R \rightarrow RCN + CNMgX}$$

Aliphatic and aromatic organomagnesium compounds reacting with cyanogen chloride also form magnesium iminohalides, which however give nitriles on boiling in water:

$$\mathrm{ClCN + RMgX \rightarrow ClC({:}NMgX)R \rightarrow RCN + ClMgX}$$

Reaction of metals with thioureas in high-boiling, indifferent media at elevated temperatures.

Transformation of isonitriles to nitriles at 200°. This method is especially suitable for the preparation of aromatic nitriles.

Decomposition of aldehyde hydrazones by heating at 180–200° in the presence of cuprous chloride, zinc chloride and other metal salts. Hydrazones of low molecular weight give small yields of nitriles, decomposition taking place largely in the direction of the formation of indoles, whereas hydrazones of higher molecular weight, such as isovaleraldehyde- or oenantholhydrazones, give good yields of nitriles.

Nitriles have also been obtained through the exchange of carboxy and cyano groups between a carboxylic acid and a nitrile. Adiponitrile has thus been made in

65% yield by heating adipic acid with about 8 moles of acetonitrile at 300° in an autoclave for ten minutes[62]:

$$HOCO.(CH_2)_4COOH + 2CH_3CN \rightarrow CN.(CH_2)_4CN + 2CH_3COOH$$

In addition to the above, there are three important general methods of preparation of nitriles; namely replacement of halogens or negative groups in organic compounds with a —CN group by reaction with alkali cyanides; Sandmeyer's method consisting essentially in the replacement of a diazo group with a —CN group; and the formation of α-hydroxy nitriles from carbonyl compounds by reaction with hydrocyanic acid in the presence of a trace of alkali. These methods are considered in their proper place in the text. Nitriles are also obtained in special cases through the interaction of hydrocyanic acid with unsaturated compounds, and the reaction of cyanogen halides with aromatic hydrocarbons in presence of aluminum chloride. These methods are also considered in the text in the proper sections. Some of the methods cited above are of little practical importance; the more important methods used for the preparation of nitriles are illustrated by examples that follow.

Preparation of Some Representative Nitriles

Inorganic Cyanides and Hydrocyanic Acid. Inorganic cyanides, which are the starting point of the preparation of many nitriles, and are of importance in industrial syntheses, may be prepared by direct synthesis or are obtained as byproducts in the coal gas and beet sugar industries.

Calcium cyanide is prepared on a large scale from calcium cyanamide, by fusion in an electrically heated furnace. Sodium cyanide is synthesized by heating sodamide with charcoal in an electric furnace. Hydrocyanic acid may be prepared by direct synthesis from ammonia and carbon monoxide, or from formamide, by catalytic dehydration, a process which is probably used on the commercial scale. Other methods for the synthesis of hydrocyanic acid have also been worked out. Large quantities of hydrocyanic acid are prepared by the pyrolytic decomposition of beet molasses; and considerable quantities of sodium cyanide are prepared from hydrocyanic acid made by this process.

Preparation of Hydrocyanic Acid. Hydrocyanic acid may be readily obtained by adding slightly more than the required quantity of a mineral acid to an aqueous solution of an alkali cyanide and distilling the highly volatile compound. Wade and Panting[1] prepared pure, anhydrous hydrocyanic acid as follows:

A cold mixture of 100 cc of concentrated sulfuric acid and an equal volume of water was added slowly to 100 grams of coarsely granular, pure potassium cyanide in a large flask connected with two U-tubes and two condensers each attached to a receiver. The U-tubes were filled with a mixture of fused calcium chloride and a dry, porous material, and were immersed in water warmed to 35°. Brine cooled to −10° was circulated through the jacket of the first condenser, while brine at −20° was circulated through the jacket of the second. The mixture of sulfuric acid and water was added at such a rate that hydrocyanic acid ran from the first condenser at the rate of about a drop a second. After all of the sulfuric acid mixture was added and the reaction abated, the liquid in the flask was heated to boiling for a short time. The greater part of the liquid collected in the receiver attached to the first condenser, only about 2 to 3% being collected in the receiver attached to the second condenser. The combined distillate, weighing about 40 grams, was further purified by treatment with a little phosphorus pentoxide and rectification over a water-bath. The quantity of pure, anhydrous hydrocyanic acid obtained was 38.5 grams, representing over 94% of the theoretically expected amount.

Synthesis of Hydrocyanic Acid. Hydrocyanic acid may be synthesized directly from nitrogen and hydrocarbons by use of the electric arc[54], though the process is apparently used on a commercial scale only in Norway where cheap water power is available. A more important synthetic method consists in the interaction of carbon monoxide and ammonia[55] or dehydration of formamide[56] at elevated temperatures in the presence of appropriate catalysts. A great variety of catalysts have been suggested for this reaction, among them the oxides of aluminum, thorium, zirconium, cerium and vanadium, and carbides of iron, silicon, titanium and zirconium. Zeolites, active carbon and bauxite have also been proposed as catalysts.

The procedure developed in Germany for the preparation of hydrocyanic acid from formamide is described as follows: Formamide is vaporized in a stream of ammonia to give a mixture consisting of 3% formamide and 97% ammonia. The mixture is passed, first through a filter packed with Raschig rings, then over a catalyst heated to 350–370°. The catalyst consists of aluminum phosphate supported on Bolus Alba. The gases emerging from the catalyst chamber are passed through a cooler, then through an absorption tower filled with Raschig rings and fed with 50% sodium hydroxide solution, where the hydrocyanic acid is absorbed quantitatively by reaction with sodium hydroxide to form sodium cyanide.

Some success has attended efforts to produce hydrocyanic acid through the interaction of ammonia and hydrocarbons at high temperatures and in the presence of catalysts[57]. Promising results have been obtained, in particular, in a process utilizing the interaction of ammonia and hydrocarbons in the presence of a limited quantity of oxygen and in contact with a platinum catalyst[58]. Finally, a study of the reaction of oxides of nitrogen with hydrocarbons in the presence of catalysts has given encouraging results[59].

Properties of Hydrocyanic Acid. Hydrocyanic acid is a colorless, mobile liquid, boiling at 25.65° under normal atmospheric pressure; it solidifies at −14.86°. The density of the liquid is 0.7150 at 0°, 0.7017 at 10°, and 0.6884 at 20°. Its vapor density is 0.969 at 31°.

The vapor pressure of the liquid at various temperatures as determined by Perry and Porter[2] is given in the following table:

Temperature °K	*Vapor Pressure mm Hg*
243.7	50.24
257.95	128.78
273	264.39
285.30	448.93
294.53	647.87
300.42	807.23

The vapor pressure at the triple-point is 140.40 mm. The critical temperature is 183.5° ± 0.1° and the critical pressure 55.0 Kg/cm^2. The molecular latent heat of vaporization is 6.76 Cal. at the boiling point; the molecular heat of fusion is 2.009 Cal. The heat of formation from the elements is −27.5 Cal.; the molecular heat of combustion is 153.6 Cal.

The surface tension of the liquid is 19.1 dynes/cm at 10.0°, 18.2 at 17.0° and 17.2 at 25.0°. The viscosity $\eta \times 10^5$ is 232.3 at 5°, 211.2 at 15.1° and 201.4 at 20.2°. The dipole moment of gaseous hydrocyanic acid is 2.1×10^{-18} e.s.u. in the temperature range 3 to 15°.

Hydrocyanic acid is miscible in all proportions with water, alcohol, ether, benzol and most other organic liquids.

Structure of Hydrocyanic Acid. The structure of the molecule of hydrocyanic acid is generally regarded to be expressed by the formula $H.C{\equiv}N$[76]. The compound undoubtedly exists in two tautomeric forms, the nitrile form just given, and the carbylamine or *iso*nitrile form $H.N{=}C$. Evidence points to the existence of both forms in liquid hydrocyanic acid, the carbylamine form in very minute quantities, possibly not more than 0.5% of the total. All efforts to isolate the carbylamine form have failed. There is evidence to indicate that certain metallic cyanides exist (in part or wholly) in the form of the *iso*cyanides[77].

Toxic Properties of Hydrocyanic Acid and Nitriles. Hydrocyanic acid is among the most toxic compounds known. Acute poisoning may be caused through inhalation of high concentrations of the vapors in air as well as through ingestion even of very dilute solution of the acid or its salts. It takes effect very rapidly and high doses may prove rapidly fatal, unless immediate measures are taken and antidotes administered. Effective antidotes have been developed recently[60].

It is possible to work with perfect safety with the acid in any of its concentrations, with the observance of simple and effective precautionary measures directed at preventing the inhalation of vapors. The fact that the anhydrous liquid and its solutions possess a very high vapor pressure even at low temperatures should be kept in mind. The best method of neutralizing the acid is by use of a large excess of cold dilute aqueous sodium hydroxide solution.

Nitriles, in general, are far less toxic than hydrocyanic acid, and danger of poisoning by them is further reduced by the fact that the vapor pressure of most nitriles is rather low at room temperature. Unsaturated nitriles, such as acrylonitrile and its derivatives, and certain chlorinated nitriles, such as monochloroacetonitrile and trichloroacetonitrile, have a toxic power approaching that of hydrocyanic acid, although they are all far less volatile than hydrocyanic acid. These nitriles will cause poisoning by penetration through the skin.

Methyl Cyanide[3], **$CH_3.CN$.** (1) To a solution of 65 grams of potassium cyanide in 60 grams of water are added in three portions 126 grams of dimethyl sulfate with good agitation; the mixture is then distilled on a water-bath, condensing and collecting the methyl cyanide formed. When no more methyl cyanide distills over, 65 additional grams of potassium cyanide are added and the mixture is carefully distilled. The product is dried with calcium chloride and fractionally distilled.

(2) A mixture of 10 grams of acetamide and 15 grams of phosphorus pentoxide is heated in a flask with a luminous flame, and the distillate condensed and

collected. The crude methyl cyanide thus obtained is mixed with half its volume of water, the mixture is saturated with potassium hydroxide; the upper acetonitrile layer is separated and rectified over a little phosphorus pentoxide.

Methyl cyanide is a colorless liquid miscible with water in all proportions. Common salt and other water-soluble salts added to its aqueous solution cause the separation of methyl cyanide. It has strong solvent power for a number of salts; thus it dissolves alkali halides and silver nitrate. Solutions of inorganic salts in methyl cyanide conduct the electric current.

Ethyl Cyanide[4], **C_2H_5CN.** To a solution of 250 grams of potassium cyanide in 500 cc of water are added 495 grams of potassium ethyl sulfate, and the mixture is heated to 115–120°, condensing the vapors. The crude ethyl cyanide thus obtained is fractionally distilled, the fractions distilling at 75 to 85° and 85 to 92° being collected separately. Phosphorus pentoxide is added to the residue in the flask and the mixture is allowed to stand six hours; then the nitrile is fractionated. The portion distilling at 96 to 98° is nearly pure ethyl cyanide. The fraction boiling at 75–85° obtained by the previous fractionation is treated with a saturated solution of calcium chloride, the oil separated and dried with calcium chloride and combined with the portion boiling at 85–92°, and the process of fractionation is repeated, again dehydrating the residue in the flask with phosphorus pentoxide and finally fractionating once more.

Ethyl cyanide forms in 85% yield when vapors of acetic acid, mixed with a slight excess of ammonia, are passed over alumina at 500°[5]. Ethyl cyanide has also been prepared in 60% yield by the dry distillation of zinc acetate with lead thiocyanate. Propionic, butyric, isovaleric, stearic and hydrocinnamic nitriles have also been made in good yield by this method from the zinc salt of the corresponding acids[6].

Ethyl cyanide is a colorless liquid with an ethereal odor, fairly soluble in water. Calcium chloride "salts out" the nitrile from its aqueous solution.

Isopropyl Cyanide[7], **$(CH_3)_2CH.CN$.** Isobutyronitrile is prepared by heating to boiling a mixture of isobutyric acid and potassium thiocyanate. The mixture is then fractionated; the fraction boiling between 190–200° is shaken with concentrated sodium hydroxide solution; the nitrile is separated and fractionally distilled. The nitrile distills at 107–108°.

***n*-Hexyl Cyanide**[8], **$CH_3(CH_2)_5CN$.** *n*-Hexyl cyanide forms, together with other products, on heating a mixture of oenanthic acid and potassium thiocyanate, and distilling the reaction product. The liquid portion of the distillate is treated with dilute caustic, the oil is separated and fractionally distilled. The nitrile distills between 175 and 178°. The nitrile may also be prepared from oenanthaldoxime by dehydration with acetic anhydride, thionyl chloride or lead oxide[9].

Allyl Cyanide[10], **$CH_2{:}CH.CH_2CN$.** A mixture of allyl iodide with an excess of potassium cyanide is heated in a sealed tube at 110° for two days; the reaction product is then washed with a little water, dried with anhydrous calcium chloride and again heated to 110° with a small quantity of potassium cyanide. The brown product is then fractionally distilled. The nitrile fraction boils between 115 and 119°; a few drops of nitric acid are added to this with stirring, then the excess acid is neutralized with potassium carbonate and the fraction is finally redistilled.

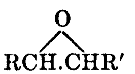
The nitrile distills between 116 and 118°. Allyl cyanide may be obtained in quantitative yield by heating a mixture of allyl bromide and cuprous cyanide on the water bath[11].

Allyl cyanide is a liquid with a pleasant odor. Hydrolyzed with concentrated hydrochloric acid at 50–60°, it forms β-chlorobutyric acid[12]. With alcohol and hydrochloric acid it forms the ethyl iminoether hydrochloride of β-chlorobutyric acid[13]. It reacts with bromine to form principally β,γ-dibromobutyronitrile, also small quantities of α,β-dibromobutyronitrile and two unsaturated monobromonitriles[14].

Allyl cyanide is converted to β-chloro- or β-bromobutyronitrile by reaction with hydrochloric or hydrobromic acid; these halonitriles, treated with powdered potassium hydroxide or with pyridine, give two isomers of crotonic nitrile[11]. Allyl cyanide reacts with alcohols in the presence of sodium alcoholates on heating for a short time. The compounds formed are of the type, $CH_3CH(OR)CH_2CN$. The methoxy-, ethoxy-, propyloxy-, *iso*propyloxy-, allyloxy-, butyloxy- and isobutyloxy-derivatives have been made. Heated with phenols in the presence of a trace of sodium ethoxide, allyl cyanide is converted to a mixture of isomeric crotonic nitriles, but no trace of phenoxynitrile forms[15].

Unsaturated Nitriles. α,β-Unsaturated nitriles have assumed considerable importance in the field of synthetic rubbers and plastics; for this reason the preparation of these compounds deserves special attention. A number of methods are available for the preparation of unsaturated nitriles. Dehydration of saturated hydroxy nitriles, or dehydrohalogenation of saturated halonitriles are among the more important. Dehydration may be brought about by heating with sulfuric acid, phosphorus pentoxide and occasionally with thionyl chloride[63]. Dehydrohalogenation may be accomplished by treatment with a tertiary base such as pyridine[64]. Dehydrohalogenation of halonitriles may also be brought about at relatively high temperatures (150–250°) by use of catalytic quantities of an amine hydrohalide[65]. Where the possibility of the formation of position or space isomers exists, such isomers are usually found simultaneously in the reaction product[67].

α-Hydroxynitriles, which may be prepared through the interaction of hydrocyanic acid with aldehydes and ketones, cannot be dehydrated catalytically, since these compounds readily dissociate when heated into hydrocyanic acid and the carbonyl compound from which they were originally prepared. β-hydroxynitriles, on the other hand, which may be obtained from oxides of the type



$$\overset{O}{\mathrm{RCH.CHR'}}$$

and hydrocyanic acid or alkaline earth cyanides may be readily dehydrated by this method. Acrylonitrile is prepared, for example, through the catalytic dehydration of ethylene cyanohydrin.

α-Hydroxynitriles, when acylated, can be pyrolytically converted to unsaturated nitriles. Cyanoethylacetate, $CH_3CH(CN)OCOCH_3$, which results from the interaction of acetaldehyde cyanohydrin and acetic anhydride may thus be readily converted to acrylonitrile. Another effective method employed for the preparation of unsaturated nitriles from α-hydroxynitriles is the replacement of the hydroxy group by chlorine, for example, through the use of thionyl chloride, and subsequent elimination of hydrogen chloride by treatment with a base[68].

Hydroxynitriles have been made from halohydroxy compounds derived from halocarbonyl compounds or haloesters by the use of the Grignard reaction. Chloroacetone has thus been converted into chlorohydroxy compounds of the type, $ClCH_2C(OH)RR'$, from which nitriles of the type, $CNCH_2C(OH)RR'$, have been obtained by reaction with an alkaline cyanide. Similar chlorohydroxy compounds have been made from ethyl chloroacetate and organomagnesium compounds[69].

Chlorinated nitriles may be prepared directly through the chlorination of aliphatic nitriles. This offers a method for the preparation of unsaturated nitriles from saturated nitriles[70].

Unsaturated nitriles may be obtained through the condensation of aldehydes or ketone with cyanoacetic acid or its ester, and subsequent decarboxylation of the resulting unsaturated cyanocarboxylic acids or esters[71].

$$RR'CO + H_2C(CN)COOH \rightarrow RR'C{:}C(CN)COOH \rightarrow RR'C{=}CHCN$$

α,β-Unsaturated nitriles have been obtained through the interaction of vapors of formaldehyde and nitriles in which a CH_2 group adjacent to the cyano group is present[72]. Unsaturated nitriles have also been obtained in good yield through the catalytic dehydrogenation of vapors of saturated nitriles in the temperature range 550–650°. The catalysts employed are oxides of vanadium or chromium[73]. α,β-Unsaturated nitriles may be obtained through the catalytic isomerization at 200–370° of unsaturated nitriles in which the double bond is further removed from the cyano group. Thus, β-methylacrylonitrile, $CH_3CH{=}CHCN$, has been prepared from allyl cyanide in 99% yield, by use of a catalyst consisting of 18% barium cyanide on 6–14-mesh active charcoal[74]. Certain unsaturated nitriles may be prepared from the corresponding halogen compounds by reaction with an alkaline cyanide or with cuprous cyanide[75]. Finally, unsaturated nitriles result from the dehydration of the amides of the corresponding acids. Fumaronitrile has thus been prepared through the dehydration of fumaric diamide with phosphorus pentoxide[66].

Crotonic Nitrile[16], $CH_3CH{:}CH.CN$. Crotonaldoxime is dissolved in ten times its weight of ether and an excess of 10% solution of acetic anhydride in ether is added; the mixture is allowed to stand at room temperature for one hour, and is then carefully neutralized with concentrated potassium hydroxide solution and extracted with small portions of ether. The ether extracts are combined and washed with caustic, carefully dried with anhydrous calcium chloride, then the ether is evaporated off and the liquid is fractionally distilled. The nitrile distills at 119°. The yield is 85% of theory.

Undecylenic Nitrile[17], $CH_2{:}CH(CH_2)_8.CN$. Undecylamide is mixed with one molecular equivalent of phosphorus pentachloride, and the mixture is gently warmed. The nitrile is isolated by fractional distillation under reduced pressure. It boils at 257° under atmospheric pressure, and at 129–130° under 14 mm. It is insoluble in water; soluble in organic solvents.

Geranic Nitrile[18], **$CH_3CH(CH_3).CH_2.CH:CH.C(CH_3):CH.CN$.** A mixture of 1 part of citraldoxime and 2.5 parts of acetic anhydride is heated under reflux for 30 minutes; the acetic acid formed in the reaction together with the excess acetic anhydride are distilled off and the residue is distilled under vacuum. Geranic nitrile is a colorless liquid soluble in alcohol, ether and chloroform. It boils at 110° under 10 mm pressure.

Cyanogen[19], **CN.CN.** An aqueous solution of 1 part by weight of potassium cyanide is added dropwise to a solution of 2 parts of crystalline copper sulfate in 4 parts of water. Toward the end, the liquid is heated on the water-bath. The cyanogen liberated is first passed through a dry flask immersed in ice, then through a calcium chloride tube. The gas is contaminated with 1 to 2% hydrogen cyanide and about 20% carbon dioxide.

Cyanogen is a gas at ordinary temperature. It condenses to a colorless liquid at −21.17° and solidifies at −27.9°. The density of liquid cyanogen is 0.9577 at −26.39°, 0.95284 at −20.85° and 0.94522 at −16.50°. The vapor pressure of cyanogen at various temperatures is given in the following table:

Temperature °*K*	*Pressure* *mm Hg*
179.94	1.7
199.05	12.79
230.27	196.7
251.77	754.0
258.26	1007.4
273.10	1828.8

The critical temperature of cyanogen is 128.3° and the critical pressure 59.6 atmospheres. The molecular heat of vaporization is 5.846 Cal. at the melting point, 5.778 Cal. at the boiling point; the heat of sublimation is 7.750 Cal.; the heat of formation from the elements is 62.9 Cal.; the molecular heat of combustion is 261.3 Cal.; the surface tension at the boiling point of the liquid is 21.98 dynes/cm.

Water dissolves four volumes of gaseous cyanogen, alcohol 26 volumes and glacial acetic acid 80 volumes at ordinary temperature. Cyanogen is an extremely toxic gas, and its vapors should not be inhaled.

Cyanoacetic Acid[20], **$CNCH_2COOH$.** To a solution of 12 parts by weight of sodium chloroacetate in 20 parts of water heated to 100°, are added 7 parts of potassium cyanide, in small portions and with adequate stirring. After the completion of the reaction, the liquid is cooled to 0° and neutralized with 1.2 parts of hydrochloric acid of specific gravity 1.18. The potassium chloride which precipitates out is filtered and the filtrate is concentrated in vacuum. On cooling the acid crystallizes.

Pure cyanoacetic acid may be obtained by hydrolyzing ethyl cyanoacetate with dilute nitric acid. 517 grams of ethyl cyanoacetate are heated at 95–100° for two to four hours under good agitation with a mixture of 500 cc of water and 50 cc of nitric acid of 1.4 specific gravity. The solution is then evaporated to a small volume and dried in a desiccator. The acid is obtained in 88% yield[51].

Ethyl Cyanoacetate[21], **$CNCH_2COOC_2H_5$.** A mixture of 100 grams of ethyl chloroacetate, 54 grams of potassium cyanide and 70 cc of methyl alcohol is refluxed four hours. The liquid is then cooled, the solid is filtered, the alcohol is distilled off and ether is added to the residue. The liquid is filtered from the solid which precipitates, the ether is evaporated off and the residue is fractionally distilled. The crude cyanethyl acetate is further purified by fractional distillation. The yield is about 50% of theory.

Malononitrile[22], **$CNCH_2CN$.** Dry, powdered cyanoacetamide is mixed intimately with an equal weight of phosphorus pentachloride and the mixture is heated under vacuum on a water-bath. Reaction sets in at 90° and is accompanied by a vigorous evolution of hydrogen chloride. When the liquid boils quietly and no more hydrogen chloride is given off, the liquid is heated in a metal bath, and the dark brown liquid is distilled *at once*. The crude nitrile is freed of phosphorus oxychloride by repeated fractional distillation. The yield is 70% of theory.

Pure malononitrile is a white, ice-like solid, melting at 29°. It boils at 219 to 220° under ordinary pressure, and at 99° under 11 mm pressure; it becomes colored on standing, even in the absence of light. It is not stable and gradually undergoes a chemical transformation on long standing.

Succinonitrile[23], **$CN.CH_2.CH_2.CN$.** A solution of 300 grams of ethylene bromide in 500 grams of alcohol is heated to boiling, and a concentrated aqueous solution of 200 grams of potassium cyanide is added dropwise with good agitation; heating is continued after the addition of all of the cyanide solution. The reaction is complete in less than two hours. The reaction mixture is cooled, the liquid is decanted from the crystals which separate, the alcohol and water are evaporated off on the water-bath, the succinonitrile is taken up with alcohol and the solution is fractionally distilled. Succinonitrile distills at 147° under 10 mm. The yield is 75 to 80% of theory.

Acetyl Cyanide[24], **CH_3COCN.** A mixture of acetyl chloride and silver cyanide is heated in a sealed tube to 100° for one or two hours; the resulting liquid is then fractionally distilled. The portion distilling between 80 and 90° is again fractionally distilled to obtain the pure nitrile which boils at 93° under atmospheric pressure. Acetyl cyanide dissolves gradually in water and reacts with it, forming hydrocyanic and acetic acids.

Acetyl cyanide has been obtained in 77% yield by heating a mixture of equimolecular quantities of acetyl bromide and cuprous cyanide on a steam bath for two hours[52].

Propionyl Cyanide[25], **CH_3CH_2COCN.** A mixture of propionyl chloride and silver cyanide is heated for a long period at 100°, and the propionyl cyanide is isolated by fractional distillation. Propionyl cyanide is a colorless, light liquid, boiling at 108 to 110°. It is decomposed by water to propionic acid and hydrocyanic acid. It assumes a yellow color on standing.

Acyl cyanides may be prepared also through the interaction of anhydrous hydrocyanic acid with acid chlorides in the presence of pyridine[52]. The nitrile may be obtained in good yield by the following procedure[53]:

A solution of the acid chloride and 4 molecular equivalents of hydrocyanic acid in ether is cooled in ice and 4 molecular equivalents of pyridine are added gradually in the course of an hour. The mixture is kept in ice-water for 12 hours; then the pyridine hydrochloride is filtered and the nitrile is isolated by distilling off the ether and pyridine, the latter under vacuum. The nitrile is purified after filtration, either by crystallization or by distillation.

Benzonitrile[26], **C_6H_5CN.** Benzenediazonium chloride is made by adding a solution of 7 grams of sodium nitrite in 200 cc of water to a strongly cooled solution of 9.3 grams of aniline and 20.6 grams of hydrochloric acid of specific gravity of 1.17 in 80 cc of water. To this is added a solution made by dissolving 25 grams of crystalline copper sulfate in 150 cc of water by the application of heat; to the warm liquid are added 28 grams of potassium cyanide. The mixture is then distilled, the distillate is extracted with ether, the ether extract is washed successively with sodium hydroxide and dilute sulfuric acid solution, the ether is evaporated off and finally the nitrile is purified by fractional distillation.

Benzyl Cyanide[27], **$C_6H_5CH_2.CN$.** To a heated solution of 60 grams of pure potassium cyanide in 55 cc of water is added gradually a mixture of 100 grams of benzyl chloride and 100 grams of alcohol, and the whole is heated on a sand bath for three hours. The liquid separates in two layers. The upper layer, consisting of a solution of nitrile in alcohol, is separated and fractionally distilled.

Cinnamonitrile[28], **$C_6H_5CH{:}CHCN$.** Cinnamonitrile is obtained by heating a mixture of two molecular equivalents of cinnamic acid and one molecular equivalent of lead thiocyanate until carbon dioxide and hydrogen sulfide cease to be evolved, and distilling the nitrile in the residue. The crude nitrile is purified by shaking with dilute caustic solution, extracting with ether, evaporating off the ether and finally purifying the nitrile by distillation.

α-Naphthonitrile[29], **$C_{10}H_7.CN$.** Three parts of sodium naphthalenesulfonate and two parts of potassium ferrocyanide, both previously dried, are thoroughly mixed and the mixture distilled in a wrought-iron tube. The crude distillate, weighing half as much as the naphthalene sulfonate, is purified by vaporizing the ammonium carbonate present by heating on a water-bath and the residue is fractionally distilled. About 70% of the crude distillate is recovered as pure nitrile.

Nitroacetonitrile[30], **$NO_2.CH_2CN$.** Methazonic acid, $NO_2.CH_2.CH{:}NOH$, is dehydrated in ether solution by means of thionyl chloride at 30–55°. After evolution of SO_2 and HCl ceases, the liquid is washed with water, dried with anhydrous calcium chloride, and the nitrile is then precipitated as the ammonium compound, m.p. 130–135°. Nitroacetonitrile is a yellowish, mobile oil, which decomposes readily on heating. It is soluble in water, ether, alcohol and benzol. Treated with sodium nitrite and sulfuric acid, it forms cyanomethylnitrolic acid, $NO_2.C({:}NOH).CN$. Nitroacetonitrile is readily chlorinated or brominated in aqueous solution to dihalonitroacetonitrile.

Trinitroacetonitrile[31], **$(NO_2)_3.C.CN$.** This compound forms when sodium fulminate is added to a mixture of equal volumes of sulfuric acid and fuming nitric acid. Trinitroacetonitrile is a camphor-like, volatile solid, soluble in ether, water and alcohol; it is decomposed by alkalies, and explodes when heated rapidly to 220°.

Dinitroacetonitrile[32]. Dinitroacetonitrile is obtained by reducing an ethereal solution of trinitroacetonitrile with hydrogen sulfide and shaking the solution with sulfuric acid. The compound is a viscous liquid from which a crystalline solid separates on standing.

Nitrocyanoacetamide, or Fulminuric Acid, $CN.CH(NO_2)CONH_2$. Nitrocyanoacetamide forms by the spontaneous decomposition of nitromalondialdehyde dioxime, $NO_2.CH(CH{:}NOH)_2$, in aqueous solution[33]; the compound may also be obtained by the oxidation of isonitrosocyanoacetamide with potassium permanganate[34].

Chloronitromalononitrile[35], $NO_2CCl(CN)_2$. Chloronitromalononitrile is formed on heating chloropicrin with an aqueous-alcoholic solution of potassium cyanide. The compound has not been obtained in the pure form.

o-Nitrobenzonitrile[61], $NO_2C_6H_4CN$. A solution of seven grams of sodium nitrite in 40 cc of water is added gradually and under good agitation, in the course of one hour, to a fine suspension of 13.8 gm of *o*-nitroaniline in 500 cc of water containing an excess of hydrochloric acid; stirring is continued one hour longer after the addition of the nitrite. The fine suspension of the diazo compound is separated from any coarse particles of unreacted nitroaniline, and is added slowly and under vigorous agitation to a solution of 25 grams of copper sulfate and 28 grams of potassium cyanide (96%) in 150 cc of water heated to 90°. This operation should be carried out under a hood with good draught. The mixture is boiled for a few minutes and is filtered hot. The crystals of nitronitrile which separate from the aqueous layer are filtered, and the residual tarry liquid containing a large portion of the nitrile is repeatedly extracted with boiling water, as long as crystals separate upon cooling the extract. The crystals of nitrile from the various extracts are filtered, dried and purified by crystallization from carbon tetrachloride followed by crystallization from boiling, moderately dilute acetic acid. The yield of pure nitrile is 70% of theory. *o*-Nitrobenzonitrile melts at 109.5°.

The fine suspension of *o*-nitroaniline is made by treating the powdered solid with 17.5 gm of conc. hydrochloric acid, stirring until reaction is complete, then adding 500 cc of water all at once.

o-Aminobenzonitrile[61], $H_2N.C_6H_4CN$. To a solution of 500 grams of stannous chloride in 425 cc of conc. hydrochloric acid and 7.5 cc of water are added with vigorous stirring, 100 grams of *o*-nitrobenzonitrile at such a rate that the temperature remains between 20 and 30°. The temperature should not be allowed to rise above 30°; external cooling should be resorted to if necessary. After the completion of the reaction, which requires a few hours, a large volume of concentrated hydrochloric acid is added and the whole is allowed to stand at 0° for twelve to eighteen hours. The precipitated aminonitrile chloride is filtered, washed with conc. hydrochloric acid and dried. The yield is 80% of theory. A small amount (5%) of aminonitrile chloride may be recovered from the mother liquors.

The free aminonitrile may be obtained by adding the chloride to an excess of moderately dilute aqua ammonia, the precipitate being then filtered, washed and dried. The crude nitrile is purified by crystallization from carbon disulfide. *o*-Aminobenzonitrile melts at 49.5°. It is soluble in alcohol, chloroform, ether and other organic solvents; it is slightly soluble in cold water, moderately soluble in boiling water.

Cyanoform[36], $CH(CN)_3$. The sodium compound of cyanoform is obtained by conducting cyanogen chloride into an alcohol solution of malononitrile and a molecular equivalent of sodium ethoxide, while the solution is cooled. The aqueous solution of cyanoform is quite stable and reacts strongly acid.

Phosphorus Tricyanide[37], $P(CN)_3$. Phosphorus tricyanide is obtained by heating a mixture of silver cyanide and phosphorus trichloride in a sealed tube at 130 to 140° for six to eight hours. The compound decomposes vigorously in contact with water, forming hydrocyanic acid and phosphorous acid.

Arsenic Tricyanide[38], $As(CN)_3$. A mixture of 7 grams of finely powdered arsenic, 22.9 grams of cyanogen iodide and 60 to 70 cc of carbon disulfide is heated at 100° in a sealed tube, from which the air is displaced by CO_2, for 20 to 30 hours. The contents of the tube are extracted with carbon disulfide; the solvent is evaporated off in an atmosphere of dry carbon dioxide. Arsenic tricyanide is rapidly decomposed by atmospheric moisture and should be stored in an atmosphere of dry carbon dioxide. Arsenic tricyanide decomposes on heating to cyanogen, paracyanogen and arsenic.

Cacodyl Cyanides[39], R_2AsCN. Cacodyl cyanides may be prepared by the following methods:

By the action of hydrocyanic acid on arsenoxides:

$$(R_2As)_2O + 2HCN \rightarrow 2R_2AsCN + H_2O$$

By the reaction of arsine chlorides with metallic cyanides:

$$R_2AsCl + NaCN[Hg(CN)_2] \rightarrow R_2As.CN + NaCl$$

By the action of cyanogen bromide on tertiary arsines:

$$R_3As + BrCN \rightarrow R_2AsCN + RBr$$

Cacodyl cyanides are similar in their properties to the corresponding chlorides; they are more or less readily hydrolyzed by water. Under certain conditions they behave as the nitriles of arsenocarboxylic acids. Thus, diphenylarsine cyanide may be hydrolyzed with sulfuric acid to $(C_6H_5)_2AsCOOH$. Aliphatic cyanoarsines are rather easily oxidized by atmospheric oxygen, while aromatic cyanoarsines do not undergo change in air[40].

Dicyanoarsines[40], $RAs(CN)_2$. Dicyanoarsines are prepared from dichloroarsines, $RAsCl_2$, and silver cyanide in benzene solution. Methyldicyanoarsine has been made by the interaction of dimethylcyanoarsine and cyanogen bromide. Dicyanoarsines are readily hydrolyzed with water into hydrocyanic acid and the oxide corresponding to the primary arsine.

Cyanamide, $H_2N.CN$. An aqueous solution of cyanamide is readily obtained by the gradual addition of a solution of 5.5 parts of lead acetate in 11 parts of water to a solution of 1 part thiourea in a 12% aqueous solution of potassium hydroxide[41].

Cyanamide in aqueous solution may also be prepared as follows: One part commercial calcium cyanamide is dissolved in four parts of cold water, the solution is cooled in ice and a current of carbon dioxide is passed through. Calcium cyanamidocarbonate forms as an insoluble deposit. This is filtered, suspended in water and decomposed with carbon dioxide, whereby calcium carbonate precipitates out, pure cyanamide remaining in solution. The solution is filtered and concentrated by distillation under vacuum[42].

Cyanamide is a solid melting at 40°. It is very soluble in water and deliquesces in humid air. It is quite soluble also in ether, alcohol, chloroform and benzene, but dissolves sparingly in carbon disulfide. It is volatile with steam.

Cyanamide is unstable and gradually changes on standing to a dimer, dicyanodiamide, $H_2NC(:NH).NH.CN$. Transformation takes place very vigorously when cyanamide is heated to 150°, with evolution of considerable quantities of ammonia and the formation of melam and mellon in addition to dicyanamide. The polymer is also formed when an aqueous solution of cyanamide is boiled down to dryness. Basic substances accelerate the polymerization of cyanamide.

Alkaline and alkaline earth salts of cyanamide absorb carbon dioxide forming the cyanamido carbonate of the metal.

Dicyanodiamide, $H_2N.C(:NH).NH.CN$. Five kilograms of crude calcium cyanamide are dissolved in ten liters of water and heated to boiling for half an hour; the hot solution is filtered, the filtrate is cooled and the crystals of dicyanodiamide are filtered and dried.

Dicyanodiamide crystallizes in rhombic plates melting at 205°. It is moderately soluble in cold water, and alcohol and is almost insoluble in ether. One hundred grams of water dissolve 2.26 grams of dicyanodiamide at 13°. Aqueous solutions of dicyanodiamide react neutral, and the compound does not form salts with acids.

N-Cyanourea[43] (Allophanonitrile), $H_2NCO.NH.CN$. One part of cyanamide and two parts of potassium cyanate are dissolved in water and the solution is allowed to stand twenty-four hours; dilute nitric acid is then added and the solution is heated in order to destroy the free cyanic acid. The cyanurea is precipitated as the silver salt by the addition of silver nitrate; the precipitate is filtered off, dispersed in warm water and decomposed by the addition of hydrochloric acid. The precipitated silver chloride is filtered off and the solution is evaporated to crystallization.

Acetyl Cyanamide[44], $CH_3CO.NH.CN$. Seventy-three grams of dry sodium cyanamide are suspended in 700 cc of anhydrous ether; 58 grams of acetic anhydride diluted with an equal volume of ether are added and the mixture is digested for three to four hours. The sodium acetylcyanamide formed, is filtered, washed with ether, dissolved in water, and from the solution silver acetylcyanamide is precipitated with silver nitrate. The silver compound is suspended in ether and decomposed with hydrogen sulfide, the pure compound being recovered by evaporating the filtered ethereal solution.

Acetylcyanamide is thus obtained in the form of a strongly acidic syrup readily soluble in water, alcohol, chloroform and ether, and insoluble in benzol. On heating it is converted to a solid, the transformation taking place violently.

Cyanic Acid[45], HOCN. Pure cyanic acid may be conveniently prepared by heating cyanuric acid in a current of carbon dioxide in a combustion tube, one end of which is sealed and bent downward at right angle. The sealed end is first heated to the proper temperature, and the flame is then gradually advanced toward the open end. The vapors that are generated are condensed by cooling in ice-salt mixture.

Cyanic acid is a gas at ordinary temperature. It has an unpleasant odor and attacks the eyes, producing tears. Liquid cyanic acid causes burns when it comes in contact with the skin. The specific gravity of the liquid is 1.140 at 0° and 1.1556 at −20°.

Gaseous cyanic acid polymerizes slowly at room temperature, rapidly at 350°. Liquid cyanic acid kept at 0° sets to a solid within an hour. This transformation takes place energetically at room temperature. The solid consists principally of cyamelide, with a small amount of cyanuric acid.

Cyanic acid is soluble in water. Dilute solutions may be kept at 0° for a considerable period without appreciable change, but at ordinary temperature decomposition takes place rapidly, the products formed being ammonia and carbon dioxide.

Thiocyanic Acid[46], **HSCN.** Twenty grams of pulverized anhydrous potassium thiocyanate are mixed with an equal quantity of phosphoric anhydride in a flask which is cooled in ice and evacuated; hydrogen is then introduced until the pressure reaches 40 to 60 mm and concentrated sulfuric acid is added drop by drop with shaking. The thiocyanic acid vapors formed are condensed in a receiver cooled with ice-salt mixture.

Thiocyanic acid is a gas at room temperature, which when cooled strongly condenses to a white crystalline mass. In the pure condition it may be kept unchanged for several hours in a sealed tube at 0°. It melts at 5°, rapidly becoming yellow. When allowed to warm up to room temperature, it rapidly changes to a yellow crystalline mass with evolution of much heat. The pure acid causes severe burns on coming in contact with the skin. Thiocyanic acid is soluble in water, alcohol and ether. Aqueous solutions containing up to 5% of the acid are stable, but solutions containing 20% of the acid are stable only for a few minutes at −15°.

Phenyl *Iso*cyanate[47], **$C_6H_5.N:C:O$.** To a solution of 5 grams of aniline in 100 cc of benzene are added slowly and under good agitation 50 grams of a 20% solution of phosgene in toluene, whereupon aniline hydrochloride separates as a crystalline mass. Another 50-gram portion of 20% phosgene in toluene is now added and the whole is gently heated under reflux until the precipitate dissolves completely. If solution is not complete after twenty or twenty-five minutes, 10 more grams of the phosgene solution should be added and boiling continued. After all the precipitate has dissolved, the benzene and toluene are distilled under vacuum. The residue is purified by distillation under vacuum. This reaction may be employed for the preparation of other aromatic isocyanates.

Methyl *Iso*cyanate[48], **$CH_3.NCO$.** To a mixture of 50 grams of technical potassium cyanate and 10 grams of anhydrous sodium carbonate are added 65 grams of freshly distilled dimethyl sulfate and the whole is heated until a vigorous reaction sets in, heating being then discontinued, as the reaction proceeds spontaneously. The vapors evolved are condensed and collected. If the reaction becomes too vigorous the vessel is cooled somewhat. Heating is resumed when the initial reaction subsides, the end of the reaction being indicated by the condensation of vapors of dimethylsulfate on the sides of the vessel accompanied with a sharp rise in temperature. The condensate is redistilled, giving 15 to 16 grams of a crude product representing a yield of 50 to 55% of the theoretical. The liquid is purified by fractionation, pure methyl isocyanate boiling between 42 and 45°.

Ethyl isocyanate has also been prepared by this method in 95% yield.

Amyl *Iso*cyanide[44], **$C_5H_{11}.N:C$.** A mixture of 15 grams of amyl iodide and 25 grams of silver cyanide is carefully heated under reflux in an oil bath maintained at 150°. As soon as reaction begins (15 min.) the flask is removed from the bath; reaction proceeds spontaneously with foaming. When foaming ceases the flask is cautiously immersed once more in the oil bath and heated until the contents appear homogenous, but heating is discontinued before they become brown. The mass is cooled and extracted thirty times with ether in order to eliminate the unreacted amyl iodide, and the silver cyanide-isonitrile compound remaining in the residue is treated with 20 grams of concentrated potassium cyanide solution, whereby the isonitrile separates as an oil and is recovered by steam distillation and purified by fractionation. The yield of pure product boiling at 137–183° under 745 mm is 60% of theory.

Other alkyl halides react with silver cyanide forming isonitriles which combine with unreacted silver cyanide to a complex; this may be decomposed by the addition of an aqueous potassium cyanide solution[50].

Methyl Thiocyanate, CH_3SCN. Equal volumes of saturated solutions of potassium methyl sulfate and potassium thiocyanate are mixed and distilled in a retort, the volume of which is ten to twelve times that of the solution. The distillate is dried over calcium chloride and fractionally distilled, the pure compound distilling between 132 to 133[51].

Properties of Various Nitriles

In the following tables are given a list of nitriles with their density, boiling and melting points whenever available. References to methods of preparation are included in the tables.

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation

	Density	*At* °*C*	*Boiling Point* °*C*	*Under* *mm*	*Melting* *Point* °*C*	*Reference*
Acetonitrile, $CH_3.CN$	0.7828	20	81.54	760	−44.4	Waldon, P., *Ber.*, **40,** 3215 (1907).
Chloroacetonitrile, $ClCH_3.CN$	1.204	11.2	126–127 (dec.)	..	......	Scholl, R., *Ber.*, **29,** 2417 (1896); Steinkopf, W., *ibid.*, **41,** 2541 (1908).
Dichloroacetonitrile, $Cl_2CH.CN$	1.374	11.4	112–113	....	....	Bisschopinck, L., *Ber.*, **6,** 731 (1873); Steinkopf, W. and Bohrmann, L., *Ber.*, **40,** 1638 (1907).
Trichloroacetonitrile, $Cl_3C.CN$	1.439	12.2	83–84	....	....	Bisschopinck, L., *Ber.*, **6,** 731 (1873); Steinkopf, W., *Ber.*, **41,** 2541 (1908).
Bromoacetonitrile, $BrCH_2.CN$	1.771	....	148–150	.....	....	Henry, L., *Compt. rend.*, **103,** 413 (1886); Steinkopf, W., *Ber.*, **38,** 2694 (1905); **41,** 2542 (1908).
Dibromoacetonitrile, $Br_2CH.CN$	....	....	67–69	24	....	Steinkopf, W., *Ber.*, **38,** 2695 (1905).
Tribromoacetonitrile, $Br_3C.CN$	....	....	170	.....	....	Broche, C., *J. prakt. Chem.*, (2) **47,** 304 (1893); (2) **50,** 100 (1894); Steinkopf, W., *Ber.*, **41,** 2542 (1908).
Iodoacetonitrile, $ICH_2.CN$	2.3065	....	182–184 (dec.)	720	....	Scholl, R., *Ber.*, **29,** 2416 (1896); Steinkopf, W., *Ber.*, **41,** 2542 (1908); Henry, *Compt. rend.*, **103,** 413 (1886).

Nitroacetonitrile, $NO_2CH_2.CN$	1.36	18				Steinkopf, W. and Bohrmann, L., *Ber.*, **41,** 1048 (1908); Steinkopf, W., *Ber.*, **42,** 619 (1909).
Dichloronitroacetonitrile, $NO_2CCl_2.CN$			39	21		Steinkopf, W., *Ber.*, **42,** 620 (1909).
Dibromonitroacetonitrile, $NO_2CBr_2.CN$			57–58	12	−30	Steinkopf, W. and Bohrmann, L., *Ber.*, **41,** 1051 (1908).
Trinitroacetonitrile, $(NO_2)_3C.CN$					41.5	Schischkow, *Ann. chim. phys.*, (3) **49,** 310 (1857).
Propionitrile, CH_3CH_2CN	0.7799	20	97.08	760		Auger, *Compt. rend.*, **145,** 1289 (1907); Hanriot, and Bouveault, *Bull. soc. chim.*, (3) **1,** 171 (1889).
β-Chloropropionitrile, $ClCH_2CH_2.CN$	1.1443	18.5	174–176	752		Henry, L., *Chem. Zentr.*, **1898** II, 22.
Butyronitrile, $CH_3.CH_2.CH_2.CN$	0.796	15	117.4	760		Dumas, *Ann.*, **64,** 334 (1848).
α-Chlorobutyronitrile, $CH_3CH_2.CHClCN$	1.044	9	142–143	760		Henry, L., *Chem. Zentr.*, **1898** II, 22.
β-Chlorobutyronitrile, $CH_3.CHCl.CH_2.CN$.	1.0772	9	175–176	760		Henry, L., *Chem. Zentr.*, **1898** II, 22.
γ-Chlorobutyronitrile, $ClCH_2.CH_2.CH_2.CN$.	1.1620	10	195–197			Henry, L., *Bull. soc. chim.*, (2) **45,** 341 (1886).
β,γ-Dichlorobutyronitrile, $ClCH_2.CHCl.CH_2.CN$.	1.314	0	113–114	25		Lespieau, R., *Compt. rend.*, **129,** 225 (1899).
γ-Bromobutyronitrile,[1] $Br.CH_2.CH_2.CH_2.CN$.			205			Gabriel, S., *Ber.*, **22,** 3336 (1889).
β,γ-Dibromobutyronitrile, $Br.CH_2CH.(Br)CH_2.CN$.	2.02	0	124–125	8		Lespieau, R., *Compt. rend.*, **137,** 262 (1903); *Bull. soc. chim.*, (3) **33,** 61 (1905).

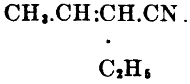
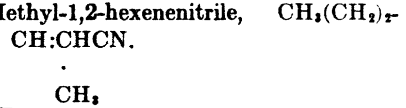
Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At °C*	*Boiling Point °C*	*Under mm*	*Melting Point °C*	*Reference*
γ-Nitrobutyronitrile, $NO_2CH_2CH_2CH_2$-CN.	1.138	12	236(dec.)	.....	....	Henry, L., *Chem. Zentr.*, **1898** II, 887.
*Iso*butyronitrile, $(CH_3)_2CH.CN$	....	....	107–108	.....	....	Letts, E. A., *Ber.*, **5,** 671 (1872).
α-Nitroso*iso*butyronitrile, $(CH_3)_2C(NO)$-CN.	....	....	....	.....	53 (dec.)	Piloty, O., *Ber.*, **31,** 1879 (1898); Piloty, O. and Schwerin, B. G., *ibid.*, **34,** 1864 (1901).
α-Nitro*iso*butyronitrile, $(CH_3)_2C(NO_2)$-CN.	....	....	97	45	35	Piloty, O., *Ber.*, **31,** 1879 (1898); Piloty, O. and Schwerin, B. G., ibid, **34,** 1864 (1901).
n-Valeronitrile, $CH_3(CH_2)_3CN$	0.8010	18	140.4	739.3	....	Lieben, A. and Rossi, A., *Ann.*, **158,** 171 (1871).
α-Chloro-*n*-valeronitrile, $CH_3CH_2CH_2$-CH(Cl).CN.	0.9995	24	160	764	....	Henry, L., *Chem. Zentr.*, **1899** I, 194.
Methyl ethyl acetonitrile, $C_2H_5CH(CH_3)$-CN.	0.8061	0	125	.....	....	Hariot, and Bouveault, *Bull. soc. chim.*, (3) **1,** 172 (1889).
Methylethylchloroacetonitrile, C_2H_5CCl-$(CH_3)CN$.	0.8969	15	55–60	32	....	Servais, *Chem. Zentr.* **1901** I, 93.
*Iso*valeronitrile, $(CH_3)_2CHCH_2CN$	0.8069	20	129.3–129.5	764.3	....	Dumas, Malaguti, and Leblanc, *Ann.*, **64,** 334 (1848).
α-Chloro*iso*valeronitrile, $(CH_3)_2CH$.-CHClCN.	0.9922	12	154	750	....	Henry, L., *Chem. Zentr.*, **1898** II, 661.
α-Bromo*iso*valeronitrile, $(CH_3)_2CH$.-CHBrCN.	....	....	175–180 (dec.)	754	....	Servais, *Chem. Zentr.*, **1901** I, 93.

Capronitrile, $CH_3(CH_2)_4CN$	0.8040	18	162–163	760	....	Braun, J. v., *Ber.*, **42**, 4549 (1909).
*Iso*capronitrile, $(CH_3)_2CH(CH_2)_2CN$	0.8075	14.2	155.48	760	....	Balard, *Ann.*, **52**, 313 (1844); Rossi, O., *Ann.*, **133**, 177 (1865).
α-Chloro*iso*capronitrile, $(CH_3)_2CHCH_2$-CHClCN.	0.984	12	172–173	755	....	Henry, L., *Chem. Zentr.* **1898** II, 661.
2-Methylbutyl cyanide, $CH_3CH_2CH(CH_3)$-$CH_2.CN$.	0.8395	10	152	.....	....	Marckwald, W. and Nolda, E., *Ber.*, **42**, 1589 (1909).
Oenanthonitrile, $CH_3(CH_2)_5CN$	0.895	22	183–184	765	....	Mehlis, T., *Ann.*, **185**, 367 (1877).
Caprylonitrile, $CH_3(CH_2)_6.CN$	0.8201	13.3	198–200	.....	....	Hofmann, A. W., *Ber.*, **17**, 1407, 1920 (1884).
α-Chlorocaprilonitrile, $CH_3(CH_2)_5$-CHCl.CN.	0.959	12	217	755	....	Henry, L., *Chem. Zentr.*, **1898** II, 662.
Pelargonic nitrile, $CH_3(CH_2)_7CN$	0.786	16	214–216	.....	....	Eichler, E., *Ber.*, **12**, 1888 (1879).
Undecylonitrile, $CH_3(CH_2)_9CN$	....	....	253–254	.....	....	Ehestädt, *Dissert. Freiburg*, **1886**.
Lauronitrile, $CH_3(CH_2)_{10}.CN$	0.8273	15	198	100	4	Lutz, E., *Ber.*, **19**, 1441 (1886).
Myristonitrile, $CH_3(CH_2)_{12}.CN$	0.8281	19	226.5	100	19	Krafft, F. and Stauffer, B., *Ber.*, **15**, 1730 (1882).
Palmitonitrile, $CH_3(CH_2)_{14}CN$	0.8224	31	251.5	100	31	Krafft, F. and Stauffer, B., *Ber.*, **15**, 1730 (1882).
Stearonitrile, $CH_3(CH_2)_{16}CN$	0.8178	41	274.5	100	41	Krafft, F. and Stauffer, B., *Ber.*, **15**, 1730 (1882).
Acrylonitrile, $CH_2{:}CH.CN$	....	....	78	.....	....	Moureu, *Ann. chim. phys.*, (7) **2**, 187, 191 (1894).
Allyl cyanide, $CH_2{:}CH.CH_2CN$	0.8351	15	119	.....	....	Pinner, A., *Ber.*, **12**, 2055 (1879).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At °C*	*Boiling Point °C*	*Under mm*	*Melting Point °C*	*Reference*
γ-Bromoallyl cyanide, $BrCH:CH.CH_2CN$	...	...	95–98	23		
α-Bromoallyl cyanide, $CH_2:CH.CHBrCN$	...	...	60	12		
Crotonic nitrile, $CH_3CH:CH.CN$	0.8259	23	118–119	...	...	Henry, L., *Chem. Zentr.*, **1898** II, 662.
α-Chlorocrotonic nitrile, $CH_3CH:CCl.CN$.	...	...	136	...	...	Sarnow, C., *Ann.*, **164**, 104 (1872).
γ-Chlorocrotonic nitrile, $ClCH_2.CH:CH.CN$.	1.1495	0	73–73.5	15	...	Lespieau, R., *Compt. rend.*, **130,** 1410 (1900).
α-Methylacrylonitrile, $CH_2:C(CH_3)CN$	0.7991	15	90–92	760	...	Henry, L., *Chem. Zentr.*, **1898** II, 662.
γ-Vinylpropionitrile, $CH_2:CH(CH_2)_2CN$	1.1803	13	140	760		
β-Ethylacrylonitrile, $CH_3CH_2CH:CH.CN$	0.8239	24	140	760		
β-Methylcrotonic nitrile, $(CH_3)_2C:CHCN$	0.8292	14	140	760	...	Henry, L., *Chem. Zentr.*, **1898** II, 662.
β-Isopropylacrylonitrile, $(CH_3)_2CH.CH:CH.CN$.	0.8266	16	154–155	754	...	Henry, L., *Chem. Zentr.*, **1898** II, 662.
α-Ethylcrotonic nitrile, $CH_3CH:C(C_2H_5)CN$.	0.8343	22	143–145	...	...	Henry, L., *Chem. Zentr.*, **1899** I, 195.
Trimethylacrylonitrile, $(CH_3)_2C:C(CH_3).CN$.	0.8447	18	155–157	760	...	Henry, L., *Chem. Zentr.*, **1899** I, 195.
β,β-Diethylacrylonitrile, $(C_2H_5)_2C:CH.CN$	...	...	90	25	...	Gardner, H. D., Jr. and Haworth, W. N., *J. Chem. Soc.*, **95,** 1965 (1909).
β-Hexyl-β-methylacrylonitrile, $CH_3(CH_2)_5.C(CH_3):CH.CN$.	...	...	130	100	...	Gardner, H. D., Jr. and Haworth, W. N., *J. Chem. Soc.*, **95,** 1964 (1909).
Undecylenic nitrile, $CH_2:CH(CH_2)_8CN$	...	...	257	...	...	Krafft, F. and Tritschler, F., *Ber.*, **33,** 3581 (1900).

Elaidonitrile, $CH_3(CH_2)_7CH:CH(CH_2)_7$-CN.	...	...	213–214	16	−1	Krafft, F. and Tritschler, F., *Ber.*, **33**, 3583 (1900).
Brassidonitrile, $CH_3(CH_2)_2CH:CH(CH_2)_{11}$-CN.	...	...	257	17	21–22	Krafft, F., and Tritschler, F., *Ber.*, **33**, 3584 (1900).
Sorbonitrile, $CH_3CH:CH.CH:CHCN$	...	...	72	20	...	Doebner, O. and Wolff, A., *Ber.*, **34**, 2222 (1901).
Diethylacrylonitrile, $(C_2H_5)_2C:CH.CN$	...	...	...	...	...	Bruylants, P., *Bull. soc. chim. Belg.*, **41**, 333 (1932).
Cis-isomer	0.82562	20°	171–172	760		
Trans-isomer	0.82619	20°	186.8–187.4	760		
α-Ethylcrotononitrile,  $\underset{C_2H_5}{CH_3.CH:\dot{C}H.CN}$	...	...	...	...	...	Bruylants, P. and Ernould, L., *Ibid.*, **41**, 262 (1932)
Cis-isomer	0.82314	20°	139–140	750		
Trans-isomer	0.83195	20°	156	750		
2,3-Pentenenitrile, $CH_3CH:CH.CH_2CN$	...	...	...	...	...	Bruylants, P., and Smoudsky, G., *Ibid.*, **41**, 273 (1932).
Cis-isomer	0.82040	20°	59–59.6	72		
Trans-isomer	0.82659	20°	143–144	761		
Propylacrylonitrile, $C_3H_7.CH:CH.CN$	...	...	...	...	...	Bruylants, P., and Ernould, L., *Ibid.*, **41**, 284 (1932).
Cis-isomer	...	...	149–150	760		
Trans-isomer	...	...	164–165	760		
1,2-Octenenitrile, $CH_3(CH_2)_4.CH:CHCN$						
Cis-isomer	0.82854	20°	74–75	11	...	Bruylants, P. and Fonteyn, M., *Ibid.*, **42**, 211 (1934).
Trans-isomer	...	...	84.7	10		
1-Methyl-1,2-hexenenitrile,  $CH_3(CH_2)_2$-$\underset{CH_3}{\dot{C}H}:CHCN.$						

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At °C*	*Boiling Point °C*	*Under mm*	*Melting Point °C*	*Reference*
Cis-isomer	0.82218	20°	46–47	10	....	Craan, A., *Ibid.*, **42**, 410 (1933).
Trans-isomer	0.82993	20°	59.4–59.6	10		
α-Butylacrylonitrile	0.82001	20°	45.8–46	10	....	Craan, A., *Ibid.*, **42**, 410 (1933).
Amylpropiolic nitrile, $CH_3(CH_2)_4C{\equiv}C.CN$	0.8508	13	194–196	.....	....	Moureu, C. and Lazennec, I., *Compt. rend.*, **142**, 213 (1906).
Hexylpropiolic nitrile, $CH_3(CH_2)_5C{\equiv}C.CN$.	0.8493	14.4	212–213	.....	....	Moureu, C. and Lazennec, I., *Compt. rend.*, **142**, 213 (1906).
Geranonitrile, $(CH_3)_2C{:}CH.CH_2.CH_2.C(CH_3){:}CH.CN$.	0.8709	20	110	10	....	Tiemann, F. and Semmler, W., *Ber.*, **26**, 2717 (1893).
Triethoxyacetonitrile, $(C_2H_5O)_3CCN$	1.0030	15.5	159–161.5	.....	....	Bauer, H., *Ann.*, **229**, 178 (1885).
Dichloromethoxyacetonitrile, $CH_3OCCl_2.CN$.	1.3885	15	148–149	732	....	Bauer, H., *Ann.*, **229**, 168 (1885).
Dichloroethoxyacetonitrile, $C_2H_5OCCl_2.CN$.	1.3394	15	160–161.5	.....	....	Bauer, H., *Ann.*, **229**, 171 (1885).
Cyanogen, CN.CN	0.866 (liquid)	17.2	−20.7	750	−34.4	Jacquemin, G., *Bull. soc. chim.*, (2) **43**, 556 (1885); *Ann. chim. phys.*, (6) **6**, 141 (1885).
Malononitrile, $CN.CH_2.CN$	1.0488	34.2	218–219	.....	29–30	Hesse, B. C., *Am. Chem. J.*, **18**, 726 (1896).
Bromomalononitrile, $BrCH(CN)_2$	....	....	....	.....	65–66	Hesse, B. C., *Am. Chem. J.*, **18**, 728 (1896).

Succinonitrile, $CN.CH_2CH_2.CN$	0.9848	63.1	265–267	....	54	Simpson, M., *Ann.*, **118,** 374 (1861); **121,** 154 (1862).
Pyrotartaric nitrile, $CH_3CH(CN)CH_2.CN$	....	....	252–254	....	12	Simpson, M., *Ann.*, **121,** 160 (1862).
Pimelonitrile, $CN(CH_2)_5CN$	0.949	18	175–176	14	....	Hamonet, J. L., *Compt. rend.*, **139,** 60 (1904); *Bull. soc. chim.*, (3) **33,** 532 (1905).
Suberonitrile, $CN(CH_2)_6CN$	0.954	18	185	....	−3.5	Hamonet, J. L., *Compt. rend.*, **136,** 246 (1903).
Azelaic nitrile, $CN(CH_2)_7CN$	....	....	195–196	19–20	....	Ssolonina, *Chem. Zentr.*, **1897** II, 848.
Adiponitrile, $CN(CH_2)_4CN$	0.951	19	295	760	....	Henry, L., *Rec. trav. chim.*, **21,** 1 (1902).
Glycolonitrile, $HOCH_2CN$	....	....	183	759	....	Klages, A., *J. prakt. Chem.*, (2) **65,** 189 (1902).
Methoxyacetonitrile, CH_3OCH_2CN	0.9373	28	120	....	....	Sommelet, M., *Compt. rend.*, **143,** 828 (1906).
Ethoxyacetonitrile, $C_2H_5OCH_2CN$	0.9093	20	135	760	....	Sommelet, M., *Compt. rend.*, **143,** 828 (1906).
Formyloxyacetonitrile, $OCHOCH_2CH$	1.182	20	172–173	759	....	Henry, L. and Dewael, , *Chem. Zentr.*, **1904** II, 1377.
Acetoxyacetonitrile, CH_3COOCH_2CN	1.103	20	177	....	....	Henry, L. and Dewael. , *Chem. Zentr.*, **1904** II, 1377.
Glycolonitrile nitrate, O_2NOCH_2CN	....	....	69–70	13	....	Scholl, R. and Steinkopf, W., *Ber.*, **39,** 4396 (1906).
α-**Methoxypropionitrile**, $CH_3CH(OCH_3)$-CN.	0.893	20	118	729	....	Gautier, *Ann. chim. phys.*, (8) **16,** 315 (1909).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At* °*C*	*Boiling Point* °*C*	*Under mm*	*Melting Point* °*C*	*Reference*
α-Ethoxypropionitrile, $CH_3.CH(OC_2H_5)$-CN.	0.878	16	131	765	...	Gautier, *Ann. chim. phys.*, (8) **16**, 315 (1909).
α-Acetoxypropionitrile, $CH_3CH(OCOCH_3)$-CN.	1.032	14	172–173	760	...	Henry, P., *Ber.*, **24** Ref. **72** (1891); Colson, A., *Bull. soc. chim.*, (3) **13**, 235 (1895).
α-Acetoxytrichloropropionitrile, Cl_3CCH-$(CN)OCOCH_3$	...	...	208	...	31	Pinner, A. and Fuchs, F., *Ber.*, **10**, 1059 (1877).
α-Acetoxybutyronitrile, $CH_3CH_2CH(CN)$-$OCOCH_3$.	1.0027	12	183	764	...	Colson, *Ann. chim. phys.*, (7) **12**, 244 (1897).
β-Hydroxybutyronitrile, $CH_3CH(OH)$.-CH_2CN.	1.0134	9	220–221	757	...	Henry, L., *Chem. Zentr.*, **1898** I, 984.
α-Acetoxyvaleronitrile, $CH_3(CH_2)_2CH$-$(CN)OCOCH_3$.	0.9696	24	194	762	...	Henry, L., *Chem. Zentr.*, **1899** I, 194.
Acetyl cyanide, CH_3COCN	...	...	93	...	...	Hübner, H., *Ann.*, **120**, 334 (1861).
Trichloroacetyl cyanide, $Cl_3C.COCN$	1.559	15	121–122	...	...	Hofferichter, P., *J. prakt. Chem.*, (2) **20**, 196 (1879).
Bromoacetyl cyanide, $BrCH_2COCN$	...	...	...	...	77–79	Hübner, H., *Ann.*, **131**, 68 (1864).
Propionyl cyanide, CH_3CH_2COCN	...	...	108–110	...	...	Claisen, L., Moritz, E., *Ber.*, **13**, 2121 (1880).
***Iso*butyryl cyanide**, $(CH_3)_2CHCOCN$	...	...	117–120	...	...	Moritz, E., *J. Chem. Soc.*, **39**, 13 (1881).
***Iso*valeryl cyanide**, $(CH_3)_2CHCH_2COCN$	...	...	145–150	...	...	Hübner, H., *Ann.*, **131**, 74 (1864).

Diacetylacetonitrile, $(CH_3CO)_2CHCN$	....	....	....	.....	50	Traube, W., *Ber.*, **31,** 2944 (1898).
Benzonitrile, C_6H_5CN	1.0102	15	190.6	760	−12.9	Sandmeyer, T., *Ber.*, **17,** 2653 (1884).
2-Chlorobenzonitrile, ClC_6H_4CN	....	....	232	.....	42–43	Montagne, *Rec. trav. chim.*, **19,** 50 (1900).
3-Chlorobenzonitrile	....	....	....	.....	39	Limpricht, H. and Uslar, L. v., *Ann.*, **106,** 35 (1858).
4-Chlorobenzonitrile	....	....	223	750	93–94	Remsen, I., Hartmann, R. V. and Muckenfuss, A. M., *Am. Chem. J.*, **18,** 169 (1896).
2,4-Dichlorobenzonitrile, $Cl_2C_6H_3CN$	....	....	....	.....	61	Gomberg, M. and Cone, L. H., *Ann.*, **370,** 182 (1909).
2,5-Dichlorobenzonitrile	....	....	....	.....	130	Noelting, E. and Kopp, E., *Ber.*, **38,** 3509 (1905).
2,6-Dichlorobenzonitrile	....	....	....	.....	49	Reich, S., *Bull. soc. chim.*, (4) **21,** 223 (1917).
2,3,5-Trichlorobenzonitrile, $Cl_3C_6H_2CN$	....	....	....	.....	87	Matthews, F. E., *J. Chem. Soc.*, **79,** 45 (1901).
2,4,6-Trichlorobenzonitrile	....	....	....	.....	77.5	Meyer, V. and Sudborough, J. J., *Ber.*, **27,** 3152 (1894).
Pentachlorobenzonitrile, C_6Cl_5CN	....	....	....	....	210	Merz, V. and Weith, W., *Ber.*, **16,** 2885 (1883).
2-Bromobenzonitrile, BrC_6H_4CN	....	....	251–253	754	51	Schöpff, M., *Ber.*, **23,** 3436 (1890).
3-Bromobenzonitrile	....	....	225	.....	38	Schöpff, M., *Ber.*, **23,** 3437 (1890).
4-Bromobenzonitrile	....	....	235–237	.....	113	Schöpff, M., *Ber.*, **23,** 3437 (1890).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At* °*C*	*Boiling Point* °*C*	*Under* *mm*	*Melting Point* °*C*	*Reference*
2-Chloro-4-bromobenzonitrile, $ClBrC_6H_3CN$.	....	....	....	.....	51–61	Blanchard, W. M., *Am. Chem. J.*, **30,** 516 (1903).
2,4-Dibromobenzonitrile, $Br_2C_6H_3CN$	....	....	....	.....	92	Claus, A. and Weil, A., *Ann.* **269,** 222 (1892).
2,5-Dibromobenzonitrile	....	....	....	.....	132	Claus, A. and Weil, A., *Ann.*, **269,** 223 (1892).
2,6-Dibromobenzonitrile	....	....	....	.....	151	Claus, A. and Weil, A., *Ann.*, **269,** 220 (1892).
3,5-Dibromo-2-amino-benzonitrile	....	....	....	.....	96.5–97	Bogert, M. T. and Hand, W. F., *J. Am. Chem. Soc.*, **25,** 941 (1908).
2,4,6-Tribromobenzonitrile, $Br_3C_6H_2CN$.	....	....	....	....	128	Sudborough, J. J., *Ber.*, **27,** 513 (1894).
2,3,4,6-Tetrabromobenzonitrile, Br_4C_6HCN.	....	....	....	.....	123	Claus, A. and Wallbaum, R., *J. prakt. Chem.*, (2) **56,** 52 (1897).
2,3,5,6-Tetrabromobenzonitrile	....	....	....	....	124	Claus, A. and Wallbaum, R., *J. prakt. Chem.*, (2) **56,** 52 (1897).
Pentabromobenzonitrile, C_6Br_5CN	....	....	....	.....	> 300	Merz, V. and Weith, W., *Ber.*, **16,** 2892 (1883).
2-Iodobenzonitrile, IC_6H_4CN	....	....	....	.....	158	Johnson, and Meade, *Am. Chem. J.*, **36,** 297 (1906).
3-Iodobenzonitrile	....	....	....	.....	41	Griess, P., *Ber.*, **2,** 370 (1869).
2-Nitrobenzonitrile, $NO_2C_6H_4CN$.	....	....	....	.....	109	Baerthlein, C. P., *Ber.*, **10,** 1713 (1877).

3-Nitrobenzonitrile	....	....	....	.....	117–118	Sandmeyer, T., *Ber.*, **18,** 1494 (1885).
4-Nitrobenzonitrile	....	....	....	.....	149	Engler, C., *Ann.*, **149,** 298 (1869).
4-Chloro-3-nitrobenzonitrile	....	....	....	.....	100–101	Claus, A. and Kurz, H., *J. prakt. Chem.*, (2) **37,** 197 (1888).
3-Chloro-4-nitrobenzonitrile	....	....	....	.....	87	Claus, A. and Kurz, H., *J. prakt. Chem.*, (2) **37,** 200 (1888).
4-Bromo-2-nitrobenzonitrile	....	....	....	.....	99	Claus, A. and Scheulen, W., *J. prakt. Chem.*, (2) **43,** 204 (1891).
4-Bromo-3-nitrobenzonitrile	....	....	....	.....	120	Schöpff, M., *Ber.*, **23,** 3439 (1890).
3-Bromo-4-nitrobenzonitrile	....	....	....	.....	104	Claus, A. and Scheulen, W., *J. prakt. Chem.*, (2) **43,** 201 (1891).
2,4-Dinitrobenzonitrile	....	....	....	.....	104–105	Cohn, P. and Friedländer, P., *Ber.*, **35,** 1267 (1902).
2,6-Dinitrobenzonitrile	....	....	....	.....	58	Claus, A. and Wallbaum, R., *J. prakt. Chem.*, (2) **56,** 67 (1897).
2-Chloro-3,5-dinitrobenzonitrile	....	....	....	.....	139	Blanksma, *Rec. trav. chim.*, **20,** 418 (1903).
o-Tolunitrile, $CH_3C_6H_4CN$	0.992	15	205	760	−13 to −14	Cahn, E. L., *Ber.*, **19,** 756 (1886).
3-Chloro-2-methylbenzonitrile	....	....	....	.....	19	Noelting, E., *Ber.*, **37,** 1025 (1904).
4-Chloro-2-methylbenzonitrile	....	....	....	.....	67	Claus, A. and Stapelberg, E., *Ann.*, **274,** 287 (1893).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At* °*C*	*Boiling Point* °*C*	*Under mm*	*Melting Point* °*C*	*Reference*
2-Chloromethylbenzonitrile, $ClCH_2C_6H_4CN$.	...	...	252	758.5	60–61.5	Gabriel, S. and Otto, R., *Ber.*, **20,** 2222 (1887).
4,6-Dichloro-2-methylbenzonitrile, $Cl_2CH_3C_6H_2CN$.	...	...	...	...	92	Claus, A. and Stapelberg, E., *Ann.*, **274,** 292 (1893).
2-Dichloromethylbenzonitrile, $Cl_2CH.C_6H_4CN$.	...	...	260	...	...	Gabriel, S. and Weise, B., *Ber.*, **20,** 3197 (1887).
2-Trichloromethylbenzonitrile, $Cl_3C.C_6H_4CN$.	...	...	280	...	94–95	Gabriel, S. and Weise, B., *Ber.*, **20,** 3198 (1887).
4-Bromo-2-methylbenzonitrile	...	...	...	...	70	Nourrisson, C., *Ber.*, **20,** 1016 (1887).
2-Propylbenzonitrile, $CH_3CH_2CH_2C_6H_4CN$	...	...	227–229	758	...	Gottlieb, J., *Ber.*, **32,** 963 (1899).
Cuminonitrile, $(CH_3)_2\overset{(4)}{CH}.C_6H_4\overset{(1)}{CN}$	0.765	14	239	758.5	...	Flatow, P., *Ber.*, **30,** 2006 (1897).
β-*Iso*duric nitrile $(CH_3)_3C_6H_2.CN$	...	...	235–238	...	55	Küster, F. W. and Stallberg, A., *Ann.*, **278,** 212 (1894).
Benzyl cyanide, $C_6H_5CH_2CN$	...	...	...	...	...	Cannizzaro, S., *Ann.*, 96, 247 (1855).
o-Chlorobenzyl cyanide, $ClC_6H_4CH_2CN$.	...	...	...	...	24	Mehner, H., *J. prakt. Chem.*, (2) **62,** 554 (1900).
Phenylchloroacetonitrile, $C_6H_5CHClCN$.	...	...	...	...	131–133	Michael, H. A. and Jeanprêtre, J., *Ber.*, **25,** 1679 (1892).
Phenyldichloroacetonitrile, $C_6H_5CCl_2.CN$.	...	...	...	...	223–224	Claisen, L., *Ber.*, **12,** 626 (1879).

o-Bromobenzyl cyanide, $BrC_6H_4CH_2CN$	...	...	...	...	Oil	Jackson, C. L. and White, J. F., *Am. Chem. J.*, **2**, 316 (1880).
p-Bromobenzyl cyanide	...	...	...	...	46–47	Wislicenus, W. and Elvert, H., *Ber.*, **41**, 4121 (1908).
p-iodobenzyl cyanide, $IC_6H_4CH_2CN$	...	...	...	...	50.5	Mabery, C. F. and Jackson, C. L., *Ber.*, **11**, 56 (1878); *Am. Chem. J.*, **2**, 253 (1880).
o-Nitrobenzyl cyanide, $NO_2.C_6H_4CH_2CN$	...	...	...	...	83–84	Salkowski, H., *Ber.*, **17**, 507 (1884).
m-Nitrobenzyl cyanide	...	...	...		61–62	Haller, G., *Ann.*, **358**, 357 (1908).
p-Nitrobenzyl cyanide	...	...	...		116	Zimmermann, M. R., *J. prakt. Chem.*, (2) **66**, 369 (1902).
Cinnamonitrile, $C_6H_5CH:CH.CN$	1.037	0	255–256	...	20.5	Krüss, G., *Ber.*, **17**, 1768 (1884).
o-Nitrocinnamonitrile, $NO_2C_6H_4CH$:-CHCN.	...	...	194–196	7–8	92	Pschorr, R., *Ber.*, **31**, 1295 (1898).
Phenylpropiolic nitrile, $C_6H_5C{\equiv}C.CN$	1.0046	41.5	228–229	...	41	Claisen, L., *Ber.*, **36**, 3671 (1903).
α-Naphthonitrile, $C_{10}H_7.CN$	1.1243	4	299	760	37.5	Boessneck, P., *Ber.*, **16**, 639 (1883); Newman, M. S., *J. Am. Chem. Soc.*, **59**, 2472 (1937).
5-Chloro-*α*-naphthonitrile	...	...	...	...	145	Ekstrand, Å. G., *J. prakt. Chem.*, (2) **38**, 147 (1888).
5-Bromo-*α*-naphthonitrile	...	...	...	...	147	Hausamann, O., *Ber.*, **9**, 1516 (1876).
5-Nitro-*α*-naphthonitrile	...	...	...	...	205	Graeff, F., *Ber.*, **16**, 2246 (1883); **14**, 1063 (1881).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At* °*C*	*Boiling Point* °*C*	*Under* *mm*	*Melting Point* °*C*	*Reference*
β-Naphthonitrile	1.0939	60/60	306.5	.....	66.5	Merz, V. and Muhlhäuser, *Ber.*, **3**, 709 (1870).
5-Chloro-β-naphthonitrile	....	....	....	.....	144	Ekstrand, Å. G., *J. prakt. Chem.*, (2) **43**, 411 (1891).
5,8-Dichloro-β-naphthonitrile	....	....	....	.....	140	Ekstrand, Å. G., *J. prakt. Chem.*, (2) **43**, 419 (1891).
5-Nitro-β-naphthonitrile	....	....	....	.....	172–173	Graeff, F., *Ber.*, **16**, 2248 (1883).
8-Nitro-β-naphthonitrile	....	....	....	.....	143	Ekstrand, Å. G., *J. prakt. Chem.*, (2) **42**, 277 (1890).
α-Naphthylacetonitrile, $C_{10}H_7CH_2CN$	....	....	191–194	18	....	Wislicenus, W. and Wren, H., *Ber.*, **38**, 507 (1905).
β-Naphthyl acetonitrile	....	....	....	.....	79–81	Blank, O., *Ber.*, **29**, 2373 (1896).
β-Anthracenecarboxylic acid nitrile	....	....	....	.....	126	Liebermann, C. and Pleus, B., *Ber.*, **37**, 648 (1904).
Phthalonitrile, CNC_6H_4CN	....	....	....	.....	141	Pinnow, J. and Sämann, C., *Ber.*, **29**, 630 (1896).
***Iso*phthalonitrile, $\overset{(1)}{CN}.C_6H_4\overset{(3)}{CN}$**	....	....	....	.....	161.5–162	Reinglass, P., *Ber.*, **24**, 2422 (1891).
Terephthalonitrile, $\overset{(1)}{C}NC_6H_4\overset{(4)}{CN}$	....	....	....	.....	223	de LaRue, W. and Müller, H., *Ann.*, **121**, 91 (1862).
Homophthalonitrile, $\overset{(1)}{C}NC_6H_4\overset{(2)}{CH_2}CN$	....	....	....	.....	81	Gabriel, S. and Otto, R., *Ber.*. **20**, 2224 (1887).

Selected List of Nitriles with Certain of Their Constants and References to Methods of Preparation (*Continued*)

	Density	*At °C*	*Boiling Point °C*	*Under mm*	*Melting Point °C*	*Reference*
Homo*iso*phthalonitrile, $\overset{(1)}{CN}.C_6H_4\overset{(3)}{CH_2CN}$	....	....	....	.....	84	Reinglass, P., *Ber.*, **24**, 2417 (1891).
Homoterephthalonitrile, $\overset{(1)}{CN}C_6H_4\overset{(4)}{CH_2CN}$	....	....	....	.....	100	Mellinghoff, W., *Ber.*, **22**, 3209 (1889).
o-Xylene dicyanide	....	....	....	.....	59–60	Baeyer, A. and Pape, C., *Ber.*, **17**, 447 (1884).
m-Xylene dicyanide	....	....	305–310	300	28–29	Kipping, F. S., *J. Chem. Soc.*, **53**, 42 (1888); *Ber.*, **21**, 42 (1888).
p-Xylene dicyanide	....	....	....	.....	98	Zincke, T. and Klippert, L., *Ber.*, **9**, 1767 (1876).
1,4-Dicyanonaphthalene	....	....	....	.....	204	Darmstaedter, L. and Wichelhaus, H., *Ann.*, **152**, 309 (1869).
1,5-Dicyanonaphthalene	....	....	....	.....	266–267	Moro, *Gazz. chim. ital.*, **26** (1), 92 (1896).
2,6-Dicyanonaphthalene	....	....	....	.....	296–297	Ebert, R. and Merz, V., *Ber.*, **9**, 604 (1876).
2,7-Dicyanonaphthalene	....	....	....	.....	267–268	Ebert, R. and Merz, V., *Ber.*, **9**, 604 (1876).

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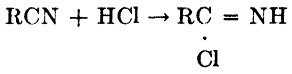
Chapter 2

Hydrolysis of Hydrocyanic Acid and Nitriles

Nitriles are generally hydrolyzed* when heated with water in the presence of strong acids or strong bases. The reactions expressing the hydrolysis are typified by the following:

$$\mathrm{RCN + 2H_2O + HCl \rightarrow RCOOH + NH_4Cl}$$
$$\mathrm{RCN + H_2O + NaOH \rightarrow RCOONa + NH_3}$$

The mechanism of acid hydrolysis is probably as follows:

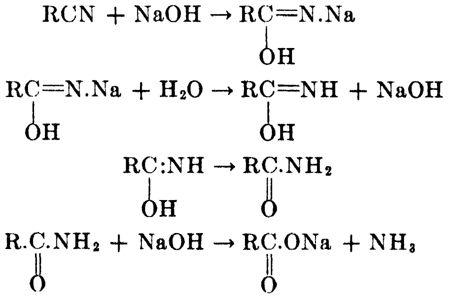


$$\mathrm{RCN + HCl \rightarrow \underset{\displaystyle \cdot \atop \displaystyle Cl}{RC} = NH}$$

$$\mathrm{RCCl{:}NH + H_2O \rightarrow RC(OH){:}NH + HCl}$$
$$\mathrm{RC(OH){:}NH \rightarrow RCO.NH_2}$$
$$\mathrm{RCO.NH_2 + H_2O + HCl \rightarrow RCO.OH + NH_4Cl}$$

The ability of certain nitriles to form iminochlorides with hydrogen chloride in inert media may be cited in support of this view.

Alkaline hydrolysis may perhaps be explained by assuming that an alkali metal imide is formed as an intermediate:



$$\mathrm{RCN + NaOH \rightarrow \underset{\displaystyle |\atop \displaystyle OH}{RC}{=}N.Na}$$
$$\mathrm{\underset{\displaystyle |\atop \displaystyle OH}{RC}{=}N.Na + H_2O \rightarrow \underset{\displaystyle |\atop \displaystyle OH}{RC}{=}NH + NaOH}$$
$$\mathrm{\underset{\displaystyle |\atop \displaystyle OH}{RC}{:}NH \rightarrow \underset{\displaystyle \|\atop \displaystyle O}{RC}.NH_2}$$
$$\mathrm{R.\underset{\displaystyle \|\atop \displaystyle O}{C}.NH_2 + NaOH \rightarrow \underset{\displaystyle \|\atop \displaystyle O}{RC}.ONa + NH_3}$$

Hydrolysis of Hydrocyanic Acid

Krieble and McNally studied the hydrolysis of hydrocyanic acid in solution with hydrochloric acid of varying concentrations and found that the rate of hydrolysis increased very rapidly as the concentration of acid was increased. Thus, with 1.95-*N* acid, less than 1% of hydrocyanic acid was hydrolyzed in

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* H. Kolbe and Frankland in 1847 were the first to carry out the hydrolysis of a nitrile to the corresponding acid. These chemists converted ethyl cyanide to propionic acid.

20 hours at 30°; with 7.84-*N* acid, hydrolysis was almost complete during the same interval. Hydrolysis was greatly accelerated as the temperature was raised; thus, at 45°, it was complete with 7.84-*N* hydrochloric acid in less than one fourth the time required at 30°. Hydrochloric acid was much more effective as a hydrolyzing agent than hydrobromic acid. The solution of hydrocyanic acid used in the tests was 0.7 molal.

The velocity constants of hydrolysis and the activities of undissociated hydrochloric acid molecule are related linearly. The reaction was demonstrated to be monomolecular[2].

Krieble and Piker who determined the velocity of hydrolysis of hydrocyanic acid at 45 and 65°, using hydrochloric, hydrobromic and sulfuric acid as hydrolyzing agents, arrived at the following conclusions:

(1) The rate of hydrolysis is independent of hydrocyanic acid concentration.

(2) The principal catalyst is the undissociated mineral acid molecule.

(3) Sulfuric acid is a poor catalyst compared with hydrochloric and hydrobromic acids, especially at higher concentrations.

(4) The relative difference in velocity between two acid concentrations is independent of temperature.

(5) The addition of sodium- or potassium chloride to hydrochloric acid, and sodium- and potassium bromide to HBr increases the velocity of hydrolysis very markedly[3].

(6) In acetic acid solution and in the presence of hydrochloric acid, the rate of hydrolysis increases rapidly as the concentration of water in the solvent decreases. Hydrochloric acid hydrolyzes hydrogen cyanide several million times faster in acetic acid than in water[4].

(7) Vapors of hydrocyanic acid are hydrolyzed with difficulty with water vapor, the reaction proceeding rapidly only at 1200°[1].

Hydrolysis of Alkali Cyanides. Metal cyanides in aqueous solution are hydrolyzed with comparative ease. Hydrolysis proceeds even at room temperature, though extremely slowly. Potassium cyanide in aqueous solution may be hydrolyzed readily in an autoclave at 180–190°[5]. Sodium cyanide in solution may be hydrolyzed under similar conditions. The products of the reaction are ammonia and alkali metal formate:

$$\mathrm{KCN} + 2\mathrm{H_2O} \rightarrow \mathrm{HCOOK} + \mathrm{NH_3}$$

Barium cyanide in aqueous solution is hydrolyzed at 200°, yielding barium formate and ammonia. Hydrolysis of calcium cyanide takes place under similar conditions.

Hydrolysis of Cyanamide

Cyanamide hydrolyzes in an aqueous acid solution to give urea. The reaction is of the first order with respect to cyanamide. When nitric acid is used as the hydrolyzing agent, the rate of reaction increases regularly with increasing concentration of acid, the logarithm of the ratio of the reaction constant to acid concentration being in linear relation with acid concentration.

Hydrochloric and hydrobromic acids show a remarkable effect: there is at first an increase in the rate with rise in acid concentration up to somewhat less than 2 Normal solution in the case of hydrochloric acid and up to about 3 Normal in the case of hydrobromic acid; there is then a steady drop in the rate with increase in acid concentration. This effect may be due to the formation of unhydrolyzable complexes between cyanamide and the acid.

Acetate buffers, di- and trichloroacetic acids show a specific catalytic action on the hydrolysis of cyanamide[117].

Solutions of cyanamide just acid to methyl red are stable over a period of months[118]. Aqueous solutions of pure cyanamide heated to 50° do not undergo change over a period of at least five days[119].

Hydrolysis of Nitriles

The hydrolysis of the nitrile group in various compounds does not take place with equal ease, but is influenced by the character of the grouping attached to the cyano group. The presence of substituents in the hydrocarbon radical also may have a marked influence.

In general, disubstituted aromatic nitriles, in which the substituents are in the ortho position with respect to the cyano group, are hydrolyzed with difficulty or not at all. This is considered to be due to the steric hindrance caused by the substituent groups. Thus, 2,4,6-trimethylbenzonitrile, 2,4,5,6-tetramethylbenzonitrile, pentamethylbenzonitrile, pentachlorobenzonitrile, 2,4,6-trimethyl-1,3-di-cyanobenzene, 1,3,5-trimethyltricyanobenzene cannot be hydrolyzed by the usual methods[6]. 2,4-Dimethylbenzonitrile is hydrolyzed by alcoholic potassium hydroxide only at 220°; hydrogen chloride does not hydrolyze the nitrile[105].

Reich found that 2,6-dichlorobenzonitrile is not hydrolyzed to the corresponding acid with 60% sulfuric acid at 150°. This nitrile may be converted to the corresponding amide with alkaline hydrogen peroxide[7].

Berger and Olivier[8] did not succeed in hydrolyzing 2,6-dimethylbenzonitrile with alcoholic potash, alkaline hydrogen peroxide and 90% sulfuric acid. Concentrated sulfuric acid reacted with the nitrile to form the amide, which was converted to the acid, with a 70% yield on heating with anhydrous phosphoric acid at 145–150° for half an hour.

Bogert and Curtin[9] were unsuccessful in their efforts to hydrolyze 2-*methoxy*-5-*acetylbenzonitrile* with hydrogen peroxide, sulfuric acid, concentrated hydrochloric acid and 5-*N* potassium hydroxide. It is of interest to note in this connection that the nitrile does not form an iminoether.

Hoch[10] observed that 2,4,6-*trimethylphenylacetonitrile* hydrolyzed very slowly and found it necessary to heat the nitrile for 40 hours with a large excess of saturated alcoholic potassium hydroxide.

Triphenylacetonitrile is hydrolyzed to the amide stage on long boiling with alcoholic potassium hydroxide[11,12].

Benzoylphenylacetonitrile resists hydrolysis under the most drastic conditions[13].

α-Diethylamino-p-methoxybenzyl cyanide, $CH_3OC_6H_4CHN(C_2H_5)_2.CN$, cannot be hydrolyzed beyond the amide stage with concentrated sulfuric acid[14].

Bruylants[15] observed that the *cis*-isomer of *ethylenic nitriles* is hydrolyzed more slowly with cold concentrated sulfuric acid than the *trans*-isomer.

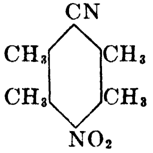
Sulokilpi[16] showed that the velocity of hydrolysis of various nitriles of the aliphatic series is increased when the radicals —OCH_3, —OC_2H_5 and —OC_3H_7 are introduced in the molecule in the α-position with respect to the cyano group.

Differences have been observed in the rates of hydrolysis of various *cyanohydrins. Cyclohexanone* and *cyclopentanone cyanohydrins* are readily hydrolyzed, 1,3-*dimethylcyclohexanone cyanohydrin* less readily, while the cyanohydrin of 1-methylcyclohexanone-2 can not be hydrolyzed at all. Acids derived from cyanohydrins also differ in the ease with which they are converted to unsaturated acids by dehydration; thus, the unsaturated acid forms with greater difficulty from alicyclic hydroxy acids as compared with aliphatic hydroxy acids[17].

The presence of negative groups in an aromatic nitrile facilitates the hydrolysis of nitriles. Thus, while great difficulty is experienced in hydrolyzing symmetrical trimethylbenzonitrile, the mono- and dinitro derivatives of this compound may be completely, though slowly, converted to the corresponding acids[18]. Similarly, when negative groups are introduced into the molecule of isoduric nitrile and the corresponding dinitrile, saponification is possible, though only by the use of energetic saponifying agents at high temperatures[18].

Long heating with alcoholic potassium hydroxide causes slight hydrolysis of *nitro-β-isoduric nitrile,* but hydrolysis proceeds to a greater extent on heating the compound with hydrochloric acid at 180 to 200° for 6 hours, some of the nitrile being converted to the amide and remaining in solution in the hydrochloric acid. *Dinitroisoduric nitrile,* $(CH_3)_3C_6(NO_2)_2CN$, may be hydrolyzed similarly with concentrated hydrochloric acid at 200 to 210°.

Cain[19] observed that the position of the nitro group in the molecule determines its effect on the reactivity of the cyano group, and showed that *nitrodurol carboxylic acid nitrile,*



can not be hydrolyzed to the corresponding acid.

There is thus evidence to suggest that while steric hindrance of groups in the proximity of the nitrile group is a factor influencing the rate of hydrolysis, substituents may also influence the rate of hydrolysis in another manner, namely through changes brought about in the affinity relationships within the cyano group. It may be stated that as a general rule hydrolysis of a nitrile group takes place with greater ease, the stronger the acid resulting from the hydrolysis.

Phenyl aryl acetonitriles cannot be hydrolyzed by boiling with aqueous mineral acids, but are converted to the potassium salts of the corresponding acids by prolonged boiling (2 hours) with alcoholic potassium hydroxide.

Kaufmann[20] found it necessary to use alkalies for the hydrolysis of *cyanoacridanes,* since acids caused the removal of the cyano group as hydrocyanic acid. Hydrolysis was accomplished by heating the nitrile with alcoholic potassium hydroxide at 160–170° in sealed tubes for ten hours. *9,10-Dimethyl(-9-cyano-acridane)* was converted to the corresponding acid by this method.

Sulfuric acid causes the hydration of the triple bond in *phenylpropiolic nitrile*, $C_6H_5C\equiv C.CN$, and simultaneously transforms the nitrile group to an amido group, forming $C_6H_5COCH_2.CONH_2$; the triple bond in *amyl-* and *hexylpropiolic nitriles* is not acted upon by sulfuric acid, but the nitrile groups are transformed to amido-groups.

Alcoholic potassium hydroxide reacts vigorously with *acetylenic nitriles*, forming both acetylenic acids and compounds of the type $RC(OC_2H_5):CH.CN$, which are subsequently hydrolyzed to the corresponding acids[21].

*Iso*succinic acid, $CH_3CH(COOH)_2$, has been prepared by alkaline hydrolysis from *α-cyanopropionic acid*[22] and phenylsuccinic acid from *phenylcyanopropionic acid*[23]. The acid hydrolysis of *alkylphenylsuccinonitriles* has been accomplished by heating in an autoclave at 130–140° for twenty to thirty hours[24].

Städel[25] prepared phenylacetic acid from *benzyl cyanide* in the following manner:

One hundred grams of benzyl cyanide were added to 300 grams of a mixture of 3 volumes of sulfuric acid and 2 volumes of water. The mixture was heated in a wide-necked flask over a direct flame until the reaction started. This was indicated by the appearance of small bubbles of vapor in the liquid. The flame was then removed. Within a few minutes the reaction became violent and the mixture boiled vigorously. The vapors were conducted into cold water. When the violent reaction ended, the mixture was heated for a few minutes. The mass was cooled, washed with water. The phenylacetic acid thus obtained contained a small quantity of phenylacetamide. If the reaction does not occur with sufficient vigor in the beginning, there is danger of the formation of considerable amide.

Triphenylacetonitrile is hydrolyzed partially to the corresponding acid by heating at 200 to 220° with a mixture of acetic acid and fuming sulfuric acid[26].

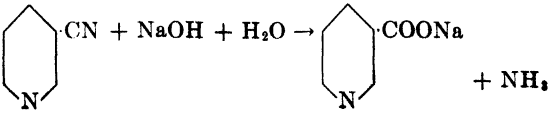
Naphthonitrile has been converted to naphthoic acid by heating at 160° under pressure with an alcoholic caustic solution; the nitrile may be hydrolyzed with sulfuric acid under normal pressure.

Besemfelder[27] hydrolyzed *β-naphthonitrile* to the corresponding acid by heating with a mixture of concentrated sulfuric acid and glacial acetic acid. This method can be successfully applied to *α-naphthonitrile*, twelve hours heating in an oil bath being required. *Naphthalene dicyanide* has been hydrolyzed with boiling alcoholic potassium hydroxide[28].

Certain very stable nitriles may be saponified by fusion with alkali. *Pyrene cyanide* yields, by this treatment, the alkali metal salt of pyrene carboxylic acid[29].

Leuchs[30] converted *α, β-dicyanobutane-δ-carboxylic ethyl ester* to the barium salt of corresponding acid by heating the nitrile with a suspension of barium hydroxide in water.

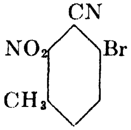
Geranic acid has been obtained by the caustic hydrolysis of *geranic nitrile*[31]. *Nicotinonitrile* has been hydrolyzed to nicotinic acid by heating with a solution of sodium hydroxide in 70% alcohol for 3 hours, a 90% yield being obtained[32]:



While Meyer states that 4-*cyanoquinoline* resists saponification, Hamer[33] has found that it may be conveniently hydrolyzed with sulfuric acid in an open vessel.

2,6-*Dinitro-p-tolunitrile* has been converted to the corresponding acid by heating with a mixture of 2 parts of sulfuric acid monohydrate and 1 part of water. The nitrile is immiscible with the acid but gradually dissolves during the heating[34].

Nitrobromotolunitrile,

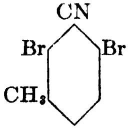


has been converted to the corresponding acid in poor yields by heating with sulfuric acid in a sealed tube to 220–300°. The acid may be obtained in better yield by heating the nitrile in a sealed tube with concentrated hydrochloric acid (25% HCl) at 220–230°. A still better yield may be obtained if the nitrile is first converted to the amide by heating with 50% sulfuric acid and the amide is then heated in a sealed tube with concentrated sulfuric acid at 240°[35].

Gräff[36,49] hydrolyzed *nitronaphthonitrile* by heating with water saturated with hydrochloric acid at 0° in a sealed tube at 150–160° for 5 hours.

Friedlander and Weisberg[37] succeeded in hydrolyzing 1,4-*nitronaphthonitrile* to the corresponding acid by boiling with baryta water. The nitrile resists the action of acids and alkalies.

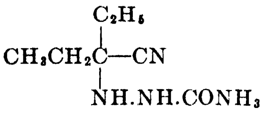
A 75% yield of dibromotoluene carboxylic acid may be obtained by boiling *dibromotolunitrile*,



with 50% sulfuric acid and heating the resulting amide with concentrated sulfuric acid at 240°[35].

For the hydrolysis of *aminonitriles*, heating to 125° for 3 hours with 5–7 molecular proportions of 40% sulfuric acid is recommended[38]. The use of sodium hydroxide solution less than 5 Normal in strength in conjunction with ammonia, or of organic acids or weak inorganic acids has also been recommended[38].

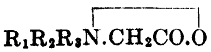
α-Ethyl-α-semicarbazidobutyronitrile,



$$CH_3CH_2\overset{C_2H_5}{\underset{NH.NH.CONH_2}{C}}—CN$$

cannot be hydrolyzed with strong acids or alkalies, as the compound decomposes on heating with these reagents[39].

Betaïn nitriles, $R_1R_2R_3N(OH)CH_2CN$, may be converted to betaïns,

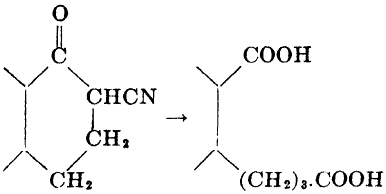


$$R_1R_2R_3N.CH_2CO.O$$

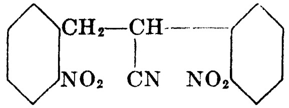
by boiling with baryta water. Betaïn nitriles may be prepared from the iodides, $R_1R_2R_3NI.CH_2CN$ and silver oxide, the iodides themselves being obtained by the combination of the secondary aminoacetonitriles, $R_1R_2N.CH_2CN$, with iodides R_3I[40].

Alanine nitrile is hydrolyzed to alanine when heated at 90–95° with barium hydroxide octahydrate; bis-(β-cyanoethyl)amine is similarly hydrolyzed to the corresponding dicarboxylic acid[107]. Heated in an autoclave at 180–225° with aqua ammonia, glycolonitrile is converted to alanine[108]. β,β'-Iminodipropionimide, $NH(CH_2CH_2CO)_2NH$, m.p. 175–176°, is obtained, together with β,β'-iminopropionic acid when $\beta.\beta$-'iminodipropionitrile is boiled with 30% aqueous sodium hydroxide[109].

The alkaline hydrolysis of α-cyano derivatives of cyclic ketones results in ring fission with the formation of dibasic acids[120]:



Hydrobromic acid is, in general, a more active hydrolyzing agent for nitriles than hydrochloric acid. Thus, *o-dinitrocyanodibenzyl*,

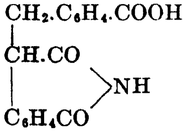


is not acted upon by boiling hydrochloric acid. The nitrile is hydrolyzed to the corresponding acid upon heating for 3 hours with hydrobromic acid of 1.47 specific gravity.

The nitrile may be hydrolyzed, and the acid isolated by proceeding as follows:

Fifteen grams of the cyanide are heated with a mixture of hydrobromic acid of 1.47 specific gravity and acetic acid, and water is then added until precipitation of the acid is complete. The crude acid is purified by dissolving with aqua ammonia and precipitating with hydrochloric acid[41].

Tricyanodibenzyl, $C_6H_4(CN)—CH(CN)CH_2.C_6H_4.CN$, does not form an acid on long-continued boiling with hydrochloric acid. One part by weight of the nitrile boiled with 10 parts by weight of hydrobromic acid of 1.47 specific gravity, gives an imido acid[42],



Cinnamaldehyde cyanohydrin, $C_6H_5CH{=}CH—CH(OH)CN$, may be converted by cold hydrochloric acid to phenyl-α-hydroxycrotonamide from which by careful hydrolysis *phenyl-α-hydroxycrotanic acid* may be obtained. Under drastic conditions cinnamaldehyde cyanohydrin is hydrolyzed[106] to *γ-benzoyl propionic acid*, $C_6H_5COCH_2CH_2COOH$.

Jansen[43] converted *acetophenone cyanohydrin* to hydratropic acid in 13% yield, by heating in a sealed tube with hydriodic acid and red phosphorus:

$$C_6H_5C(CH_3)(OH)CN \rightarrow C_6H_5C(CH_3)(OH)COOH \rightarrow C_6H_5CHCH_3.COOH$$

Acetophenone cyanohydrin may be hydrolyzed to atrolactic acid (α-phenyl lactic acid), m.p. 93.5–94°, by means of cold concentrated hydrochloric acid. When the cyanohydrin is boiled with concentrated hydrochloric acid and the product of the reaction is treated with sodium hydroxide, tropic- or α-phenyl-β-hydroxypropionic acid is obtained[44]:

$$C_6H_5C(OH)(CN)CH_3 \rightarrow C_6H_5C(:CH_2)COOH \rightarrow C_6H_5CH(CH_2Cl).COOH \rightarrow C_6H_5CH(CH_2OH).COOH$$

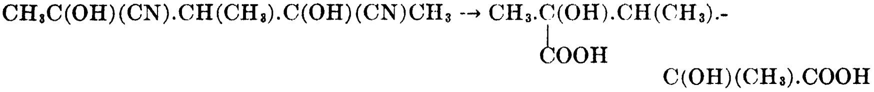
Pictet and Gams[45] converted *dimethoxymandelonitrile* to homoprotocatechuic acid by refluxing the nitrile with a tenfold quantity of hydriodic acid of 1.5 specific gravity.

Claisen[46] observed that when *benzoyl cyanide* was hydrolyzed by boiling with concentrated hydrochloric acid only benzoic acid was obtained. When, however, the cyanide was allowed to react with the acid at room temperature for several days and then heated to 70° for a short time, phenylglyoxylic acid was obtained:

$$C_6H_5CO.CN \rightarrow C_6H_5CO.COOH$$

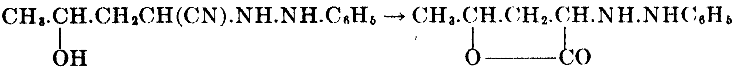
The reaction was shown to proceed in steps, the amide being first formed. Claisen found that the amide existed in three isomeric forms.

Zelinsky and Tschugaew[47] obtained trimethyldihydroxyglutaric acid by the hydrolysis at room temperature of *methylacetylacetone dicyoanhydrin:*



$$CH_3C(OH)(CN).CH(CH_3).C(OH)(CN)CH_3 \rightarrow CH_3.\underset{\displaystyle COOH}{\underset{|}{C}}(OH).CH(CH_3).C(OH)(CH_3).COOH$$

Miller and Plöchl[48] hydrolyzed *β-ethylhydroxy-α-phenylhydrazinopropionitrile* with cold hydrochloric acid to the lactone of α-phenylhydrazino-γ-hydroxyvaleric acid:



$$CH_3.\underset{\displaystyle OH}{\underset{|}{CH}}.CH_2CH(CN).NH.NH.C_6H_5 \rightarrow CH_3.\underset{\displaystyle O\text{———}}{\underset{|}{CH}}.CH_2.\underset{\displaystyle CO}{\underset{|}{CH}}.NH.NHC_6H_5$$

Kohlentechnik[50] hydrolyzed *glycolic nitrile* with aqueous hydrochloric acid at 80°.

Benzonitrile is converted to dibenzimidoxide, $(C_6H_5CNH)_2O$, when it is dissolved in benzene, a little cold concentrated sulfuric acid is added and the whole kept for 24 hours. The compound may be isolated by extracting with water, and adding sodium hydroxide to the solution[51].

Sudborough[52] prepared the amide of the 2,4- and 2,5-dibromobenzoic acids from the corresponding nitriles by heating one hour at 120 to 130° with 25 to 30 parts by weight of 90% sulfuric acid.

Krafft and Karstens[53] found that *o*-tolunitrile hydrolyzes more slowly with fuming sulfuric acid than *p*-tolunitrile, in each case the amide being the result of hydrolysis.

Mandelonitrile is readily converted to mandelamide or mandelic acid by aqueous hydrochloric acid[54]:

$$C_6H_5.CH(OH)CN + H_2O + HCl \rightarrow C_6H_5.CH(OH)CONH_2.HCl$$

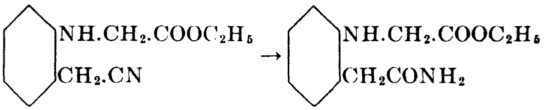
$$C_6H_5.CH(OH).CONH_2.HCl + H_2O \rightarrow C_6H_5CH(OH)COOH + NH_4Cl$$

The amide partially condenses with free benzaldehyde, normally present in mandelonitrile, to form benzalmandelamide (m.p. 194°), which is identified in the final product:

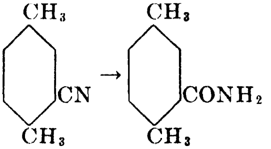
$$C_6H_5.CHO + H_2NCO.CH(OH)C_6H_5 \rightarrow C_6H_5.CH{=}N.CO.CH(OH).C_6H_5 + H_2O$$

Mandelamide is slightly soluble in water, readily soluble in alcohol. It can best be crystallized from dilute alcohol. The compound melts at 190°. It is readily converted to mandelic acid by boiling with hydrochloric acid.

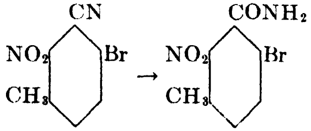
When one part of *ω-cyano-o-methylphenylglycine ethyl ester* is mixed at ordinary temperature with five parts of concentrated sulfuric acid, and the mixture, after being allowed to stand for several hours, is poured in ice-water, *o*-methylphenylglycine ethyl ester ω-carboxylic acid amide is obtained in almost quantitative yield[55]:



Schmid and Decker[56] obtained the amide of *p*-xylylcarboxylic acid by heating the nitrile with 90% sulfuric acid on a water bath for one hour:



Claus and Herbabny[35] converted *nitrobromotolunitrile* to the amide of the corresponding acid by heating it with 20 times its weight of 50% sulfuric acid for 8 to 10 hours:



Krieble and Noll[57] determined the velocity constants of hydrolysis of a number of nitriles with hydrochloric and sulfuric acids. The constants were calculated on the basis of the monomolecular reaction,

$$R.CN \rightarrow R.COOH$$

The results were as follows:

	H_2SO_4		HCl		
	4 Molal	*6 Molal*	*4 Molal*	*6 Molal*	*8 Molal*
CH_3CN	2.6	6	2.1	7.7	39
CH_3CH_2CN	4.6	9.1	3.6	14.4	78
$COOH.CH_2CN$	1.2	2.6	1.2	8.3	62
$CH_3CH(OH).CN$	6.1	17.5	28	259	1022
$CH_2(OH).CH_2.CN$	2.7	6.3	1.9	6.6	35

There was no relationship between the acidity as determined by indicators and the velocity of hydrolysis.

Formation of Amides by Alkaline Hydrolysis. Nitriles which resist the action of other hydrolyzing agents are converted, almost without exception, to the corresponding amides on prolonged heating with alcoholic caustic.

Formation of Amides by Acid Hydrolysis. If the mechanism suggested for the acid hydrolysis of nitriles is correct, at some stage in the hydrolysis the amide is formed. The amide forms in effect and may be isolated in many instances when the hydrolysis is carried out in the cold, using concentrated hydrochloric or sulfuric acid; this is the case, for example, with cyanohydrins.

By adding concentrated sulfuric acid carefully and with cooling to α-anilidopropionitrile, allowing the mixture to stand and finally adding water, the amide of anilidopropionamide may be obtained and can be separated by the addition of ammonia[58].

Phenyl-α-hydroxycrotonic amide (styrylglycolic amide) has been prepared from cinnamic aldehyde cyanohydrin, by the action of a mixture of hydrochloric and sulfuric acids[59]:

$$C_6H_5CH{=}CH.CH(OH).CN \rightarrow C_6H_5.CH{:}CH.CH(OH).CONH_2$$

Mandelamide may be prepared by digesting mandelonitrile with an excess of cold concentrated hydrochloric acid[60].

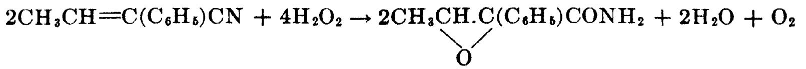
Conversion of Nitriles to Amides with Alkaline Hydrogen Peroxide. Nitriles, in general, are converted to amides when treated with 3% alkaline hydrogen peroxide[62]. Even nitriles that resist saponification with acids, such as α-naphthonitrile and *o*-tolunitrile, may be converted to the corresponding amides by this treatment, using a somewhat more concentrated hydrogen peroxide (*e.g.*, 6%)[61,63]. Cyanogen, which is ordinarily resistant to hydrolyzing agents, has been converted quantitatively to oxamide by this method[62]. Nitronaphthonitrile, which cannot be converted to the amide with acids or alkalies, yields the amide readily with alkaline hydrogen peroxide in alcohol solution[63]. The reaction takes place best in alkaline solution and at a temperature of 40°. Good yields are generally obtained when the resulting amide is insoluble in water.

The more resistant nitriles may be converted to the amide by the use of an excess of hydrogen peroxide or of a concentrated solution of the peroxide. While the method appears to be of general applicability, the yield of amide varies according to the character of the nitrile, nearly quantitative yields being obtained in some cases, and very small yields in others.

Piperonylamide has been made by this method from piperonyl nitrile, $NC.C_6H_3{:}O_2CH_2$.

Six grams of potassium hydroxide are dissolved in 600 to 650 cc of 3% hydrogen peroxide and 20 grams of the nitrile are added in small portions with gentle warming and agitation. After 30 to 40 minutes, the nitrile dissolves completely. On cooling, the amide crystallizes out. Piperonic acid forms simultaneously[64].

α-Phenylcrotononitrile is converted almost quantitatively to α, β-phenylglycidamide with hydrogen peroxide in aqueous acetone in the presence of sodium carbonate:

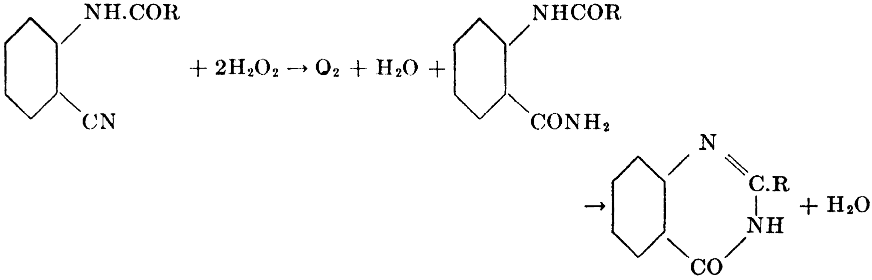


$$2CH_3CH{=}C(C_6H_5)CN + 4H_2O_2 \rightarrow 2CH_3\underbrace{CH.C}_{O}(C_6H_5)CONH_2 + 2H_2O + O_2$$

α,β-Ethylenic nitriles do not form glycidamides with hydrogen peroxide; thus, cinnamonitrile and allyl cyanide give the corresponding unsaturated amides. α-Phenylcrotonamide and α-phenyl-β-n-propylacrylamide are not acted upon by hydrogen peroxide. The formation of oxidoamides[65] appears to be restricted to nitriles with the grouping $>C{=}C{-}CN$.

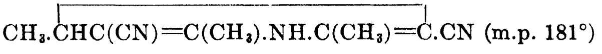
Fumaronitrile gives fumaramide, m.p. 267°[110].

Acyl anthranilic nitriles acted upon by hydrogen peroxide give 2-alkyl-4-ketodihydroquinazolines:



Methyl-, ethyl-, isopropyl- and isobutyl-derivatives have been prepared[111]. *Nicotinonitrile* gives nicotine amide in low yield[116].

Diacetonitrile is not converted to an amide by hydrogen peroxide, but gives 2,4,6-trimethyl-3,5-dicyanodihydropyridine,



$$\overbrace{CH_3.CHC(CN){=}C(CH_3).NH.C(CH_3){=}C}.CN \text{ (m.p. 181°)}$$

in a small yield. Iminodipropionitrile, $HN(CH(CH_3)CN)_2$, gives the half acid amide, $HOCO.CH(CH_3)NH.CH(CH_3)CONH_2$, in a small yield[112].

Hydrolysis of Amides to the Corresponding Acids. *Bouveault's Method.* Bouveault's method[66] offers a means of converting amides which cannot be directly hydrolyzed to the corresponding acids. The method consists in decomposing the amide in solution in concentrated hydrochloric acid by means of sodium nitrite. Meyer[67] prepared triphenylacetic acid from triphenylacetonitrile by this method, proceeding as follows:

A solution of 0.2 gm of sodium nitrite in 1 cc of water was added to 0.2 g of amide dissolved in 1 gram of concentrated hydrochloric acid, cooled in an ice-water bath, and the mixture was warmed slowly on a water-bath. At 60 to 70° a rapid evolution of nitrogen occurred. The reaction was complete when the temperature reached 80 to 90°. The solution was then heated for 3 to 4 minutes on a boiling water bath. On cooling and adding fragments of ice to the solution a yellow precipitate was obtained. This was filtered, dissolved in dilute caustic soda and reprecipitated by the careful addition of sulfuric acid. The product was purified by crystallization from acetic acid.

In Gattermann's modification of Bouveault's method, the amide is dissolved in hot concentrated acid and to the solution is added 10% sodium nitrite solution. It is important for the success of this method that the nitrite solution be introduced deep in the hot solution of the amide by means of a pipette drawn to a fine point. After cooling, the reaction product is extracted with ether, the extract is shaken with aqueous sodium hydroxide and the acid is precipitated from the latter by the addition of a dilute mineral acid.

Hydrolysis with Phosphoric Acid. Berger and Olivier[68] found that amides, formed by the hydrolysis of nitriles with sulfuric or other strong mineral acids which resisted further hydrolysis, could be converted to the corresponding acids by heating at 145 to 150° with 100% phosphoric acid. Thus a 70% yield of 2,6-dimethylbenzoic acid was obtained by heating 2,6-dimethylbenzamide with twice its weight of phosphoric acid for half an hour. Phosphoric acid of appreciably lower strength was found to be ineffective.

Dehydration of Amides to Nitriles

The hydrolysis of nitriles is a reversible process, and the conditions may be adjusted so as to favor the conversion of amides to nitriles. High temperatures bring about this transformation. The reaction may be catalytically accelerated.

Van Epps and Reid[69] investigated the catalytic dehydration of nascent acetamide from acetic acid and ammonia reporting a yield of 85% at 500°. Mailhe prepared nitriles of saturated and unsaturated acids from the corresponding esters and ammonia, using thoria or alumina as a catalyst and working in the temperature range 480 to 500°. The saturated nitriles prepared were[70]: acetonitrile, propionitrile, butyronitrile, isovaleronitrile, capronitrile, benzonitrile, tolunitriles, phenylacetonitrile and naphthonitriles[70]. The unsaturated nitriles prepared were the following[71]:

Crotonic nitrile, $CH_3CH{=}CH.CN$, boiling at 118–120°
Oleic nitrile, $C_{17}H_{33}CN$, boiling at 330–335°
Elaidic nitrile, $C_{17}H_{33}CN$, boiling at 335–340°
Cinnamic nitrile, $C_6H_5CH{=}CHCN$, boiling at 254°

Mailhe[72] also prepared nitriles by passing a mixture of an acid chloride and ammonia over alumina catalyst at 490–500°.

This author[73] investigated the reverse reaction under the same conditions, and successfully prepared the ammonium salts of the corresponding acids from the nitriles in the presence of thoria or alumina catalyst at 420°.

Nitriles have been prepared also by dehydrating a mixture of an aldehyde and ammonia over thoria catalyst at 420 to 440°. Propionitrile has been prepared in this manner from propionaldehyde. Isobutyronitrile, isovaleronitrile, benzonitrile and anisic nitrile have also been made from the corresponding aldehydes[74].

Mitchell and Reid[75] showed that silica gel is a very efficient catalyst for the dehydration of amides to nitriles. These authors reported the following yields of nitriles, calculated on the basis of the quantities of acid used in the preparation of the amides:

	% *Yield*
Methyl cyanide	95
Ethyl cyanide	85
n-Propyl cyanide	90
n-Butyl cyanide	80
*Iso*butyl cyanide	94
n-Pentyl cyanide	90
n-Hexyl cyanide	93
n-Undecyl cyanide	55
Benzyl cyanide	87
Phenylethyl cyanide	81
Palmitonitrile	0

From esters of the corresponding acids, they obtained the following yields of nitriles:

	% *Yield*
Methyl cyanide	87
n-Propyl cyanide	75
Phenyl cyanide	77

The catalyst retained its activity for a long period when ammonium salts of the acids were dehydrated, but lost its activity comparatively rapidly when the starting materials were the esters. The optimum operating temperature was found to be 500°[75].

Norris and Klenda[76] dehydrated amides in the presence of aluminum chloride or the double compound, $NaCl.Al.Cl_3$, and reported the following yields of nitriles:

	% *Yield*
Methyl cyanide	91
Benzyl cyanide	52
n-Amyl cyanide	63
Phenyl cyanide	97
o-Chlorophenyl cyanide	93
p-Tolyl cyanide	89
p-Nitrophenyl cyanide	29
2,6-Dichlorophenyl cyanide	67
2,4,6-Trichlorophenyl cyanide	
α-Naphthyl cyanide	79
β-Naphthyl cyanide	80

Biggs and Bishop[77] prepared sebacic nitrile by the catalytic dehydration of sebacic amide. A certain amount of the half nitrile of sebacic acid formed at the same time.

Ralston and co-workers[78] prepared the nitriles of higher fatty acids, such as palmitic and stearic nitriles by heating the ammonium salts of the acid in the absence of any catalyst at 330° in a current of ammonia.

m-Nitrobenzonitrile has been obtained by the action of thionyl chloride on *m*-nitrobenzamide:

$$NO_2.C_6H_4CONH_2 + SOCl_2 \rightarrow NO_2C_6H_4CN + SO_2 + 2HCl$$

On adding 10 grams of thionyl chloride to an equal weight of the amide and heating the mixture after the first reaction is over until the solution becomes clear, 80 to 90% yield of the nitrile may be obtained. In benzol solution the reaction proceeds partially[79].

The preparation of many nitriles through the dehydration of the corresponding amides has been protected by patents[121].

Reaction of Nitriles with Hydrogen Sulfide

Nitriles react with hydrogen sulfide under pressure in anhydrous solvents to form thioamides[80]:

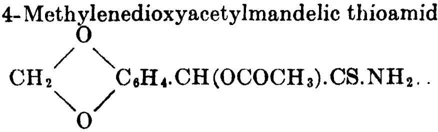
$$RCN + H_2S \rightarrow RCS.NH_2$$

Ammonium acid sulfide catalyzes the reaction. Kindler[81] showed that dimethyl ammonium acid sulfide is a better catalyst and that alkali metal acid sulfides are still better. The yields of thioamide obtained by Kindler from various nitriles are presented in the following table:

Compound	*Temperature, °C*	*Duration of Reaction*	*Yield of Thioamide, %*
Acetonitrile	60	1½ days	66
Propionitrile	38	1½ days	43
p-Tolunitrile	90	5 hours	78
β-Naphthonitrile	70	3 hours	88
Benzyl cyanide	70	3½ hours	83
β-Phenylpropionitrile	60	12 hours	64
Acetylmandelonitrile	60	12 hours	70

By the same reaction malonthioamide[113], thiobenzamide[82], aminobenzothioamide[83], acetylamino and acetylaminobenzenesulfoaminobenzothioamides[114], terephthalothioamide[115], naphthothioamide[84], cumothioamide[85], thioxamethane[86], phenylacetothioamide[87] and phenylaminothioacetamide[88] have been prepared from the corresponding nitriles.

Acetylated cyanohydrins have been converted to thioamides by reaction with hydrogen sulfide in alcoholic solution containing ammonium sulfide. By this method, Albert[89] prepared the following thioamides:

	M.P. °C	*Yield* %
α-(Acetyloxy)-isobutyrothioamide, $(CH_3)_2C(OCOCH_3).CS.NH_2$	123	50
3,4-Methylenedioxyacetylmandelic thioamide,  $CH_2(O)_2C_6H_4.CH(OCOCH_3).CS.NH_2$	145	87
Acetylmandelic thioamide, $C_6H_5CH(OCOCH_3)CS.NH_2$	105	8

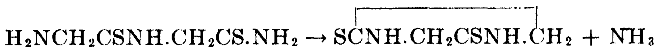
Olin and Johnson[90] prepared benzoyloxythioacetamide, $C_6H_5COOCH_2.CSNH_2$; benzoyllactothioamide, $C_6H_5COOC(CH_3).CSNH_2$; and α-benzoyloxy*iso*butyrothioamide, $C_6H_5COO.C(CH_3)_2.CSNH_2$, from the benzoylated cyanohydrins of formaldehyde, acetaldehyde and acetone using triethanolamine as a catalyst.

o-Nitrobenzoylmandelic thioamide reacts with hydrogen sulfide in ethyl alcoholic solution in the presence of ammonium sulfide to form *o*-hydroxylaminobenzoylmandelic thioamide (m.p. 159–164° dec.) in 77% yield. *o*-Nitrobenzoylthioamide may be prepared from the acetylated nitromandelonitrile and thioacetic acid[91].

Hydrogen sulfide reacts with aminoacetonitrile to form 2,5-dithiopiperazine in small yield[92]:

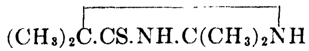
$$H_2NCH_2CN + H_2S \rightarrow H_2N.CH_2.CS.NH_2$$

$$2H_2NCH_2CSNH_2 \rightarrow H_2NCH_2CSNH.CH_2.CSNH_2 + NH_3$$



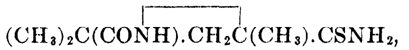
$$H_2NCH_2CSNH.CH_2CS.NH_2 \rightarrow SCNH.CH_2CSNH.CH_2 + NH_3$$

Aminopropionitrile reacts similarly to form 3,6-dimethyl-2,5-dithiopiperazine in small yield[93]. α-Aminoisobutyronitrile reacts with hydrogen sulfide to form a compound of the empirical formula, $C_7H_{14}N_2S$, probably



$$(CH_3)_2C.CS.NH.C(CH_3)_2NH$$

in low yield[94]. α-Amino-α-methylthiopyroterebinic amide, $(CH_3)_2C{:}CHC(CH_3)(NH_2).CSNH_2$ (m.p. 220°) has been obtained from mesityloxide, $(CH_3)_2C{:}CH.CO.CH_3$, by reaction with hydrocyanic acid and hydrogen sulfide in presence of ammonia. Mesitonitrile cyanohydrin, $(CH_3)_2.C(CN).CH_2.C(OH)(CN).CH_3$, gives thiomesitylic acid amide,



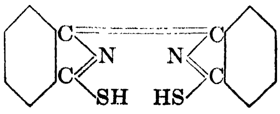
$$(CH_3)_2C(CONH).CH_2C(CH_3).CSNH_2,$$

by reaction with hydrogen sulfide in the presence of ammonia[95].

Kindler and Treu[96] studied the influence of substituents in aromatic nitriles on the ease of formation of thioamides. They observed that, in general, the more negative the character of the substituent was, the more readily the nitrile formed a thioamide. Thus, the nitriles ranged as follows in increasing order of reactivity: p-$CH_3OC_6H_4CN$ < p-$CH_3.C_6H_4.CN$ < C_6H_5CN < p-$BrC_6H_4.CN$ < m-BrC_6H_4CN. Setting the reaction velocity of benzonitrile as 100, the relative velocities of formation of thioamides from various nitriles were as follows:

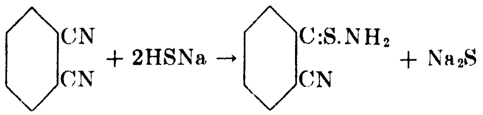
C_6H_5CN	100.0
p-$CH_3O.C_6H_4CN$	41.6
p-$CH_3C_6H_4CN$	51.9
p-$I.C_6H_4CN$	518.0
p-$Br.C_6H_4CN$	451.0
m-$Br.C_6H_4CN$	831.0
p-$Cl.C_6H_4CN$	493.0

Phthalonitrile reacts with hydrogen sulfide in alcoholic solution containing ammonia to form a bimolecular isoindole,

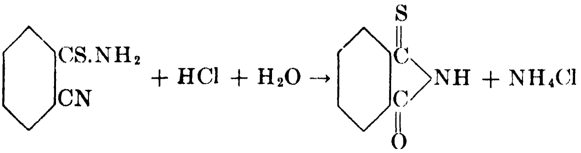


which condenses with methylene compounds with elimination of hydrogen sulfide[97].

Phthalonitrile reacts with sodium acid sulfide to form *o*-cyanothiobenzamide in good yield:



This substance is converted by hydrochloric acid to monothiophthalimide[98]:



Bernthsen[99] prepared thiobenzamide and thioacetamide by the action of an alcoholic solution of ammonium hydrogen sulfide upon benzonitrile and acetonitrile.

Higher aliphatic thioamides may be obtained through the interaction of the corresponding nitriles and ammonium sulfide in a non-aqueous medium and under pressure, at 150–160°:

$$RCN + H_2S(NH_3) \rightarrow RCS.NH_2(+NH_3)$$

Thiostearamide (m.p. 82 3°), thiomyristamide (m.p. 87–88°) and thiopalmitamide (m.p. 93–94°) were prepared by this method[100].

Signaigo[101] prepared thiols from nitriles by reaction with hydrogen sulfide in the presence of hydrogen under pressures of 500 to 5,000 pounds per square inch at temperatures of 100 to 200° in the presence of catalysts:

$$CH_3(CH_2)_{10}.CN + H_2S + 2H_2 \rightarrow CH_3(CH_2)_{10}.CH_2SH + NH_3$$

Cyanamide reacting in ethereal solution with hydrogen sulfide gives thiourea[122]. Thiourea also results when hydrogen sulfide is passed through an aqueous solution of cyanamide and ammonium acid sulfide heated to 50–85°[123]. The compound is also obtained in good yield when hydrogen sulfide and carbon dioxide are conducted at room temperature through an aqueous solution of calcium cyanamide[124].

Substituted cyanamides in alcoholic solution also readily react with hydrogen sulfide in the presence of ammonium sulfide to form *asym.* thioureas[125].

Reaction of Nitriles with Hydrogen Selenide

Dechend[102] prepared selenobenzamide, $C_6H_5CSeNH_2$ (m.p. 115°), by conducting a current of hydrogen selenide into a weakly ammoniacal alcoholic solution of benzonitrile. Becker and Meyer[103] prepared *p*-methylselenobenzamide by the same method and found that the ortho- and meta-tolunitriles reacted poorly with hydrogen selenide. Kindler obtained phenylselenoacetamide in quantitative yield by the reaction of benzyl cyanide with hydrogen selenide. Reaction with acetonitrile proceeded incompletely, and a 17% yield of selenoacetamide was obtained[104]. The reaction of hydrogen selenide with nitriles should be carried out in the absence of air, since hydrogen selenide is readily oxidized in air.

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Chapter 3

Action of Strong Mineral Acids on Nitriles

Reaction of Acids with Hydrocyanic Acid

Hydriodic and hydrobromic acids are readily absorbed by hydrocyanic acid and combine with this compound to form crystalline solids[1]. These compounds have been shown to be sesqui halides, $2HCN.3HX$.

Hydrogen chloride dissolves only slightly in hydrocyanic acid at ordinary temperature, and little or no apparent change occurs even on prolonged passage of the gas through hydrocyanic acid.

Gautier[2] obtained a white solid by saturating anhydrous hydrocyanic acid at −15° with hydrogen chloride, then alternately warming and cooling the liquid. He considered this compound to be $HCN.HCl$. Other investigators who repeated Gautier's work failed to obtain a compound with a definite composition.

Combination takes place in the cold, though very slowly upon saturation of liquid hydrocyanic acid with hydrogen chloride. The compound formed has been identified as the sesquichloride.

Hydrocyanic acid in solution in certain solvents, such as ethyl formate, ether or glacial acetic acid at −10 to −15°, combines readily with hydrogen chloride[3] to form the sesquichloride, $2HCN.3HCl$. Gattermann and Schnitzspahn[4] demonstrated that the compound is the hydrochloride of dichloromethylformamidine, $CHCl_2.NH.CH{:}NH.HCl$. Hydrobromic acid also forms the dihalomethylformamidine hydrohalide[6].

The sesquichloride decomposes when heated under vacuum, to form chloromethyleneformamidine, $ClHC{:}N.CH = NH$; the latter heated with quinoline gives iminoformyl isocyanide, $NHCH.NC$, in almost quantitative yield[6].

Hinkel and Dunn[6] prepared *chloromethyleneformamidine* as follows:

The sesquichloride was prepared by saturating a well-cooled solution of hydrocyanic acid in anhydrous ether with hydrogen chloride. The crystals were filtered rapidly, washed with ether and immediately transferred to a desiccator. The sesquichloride was then heated over a steam bath in a flask connected to a horizontal glass air-condenser and the compound was distilled under vacuum. The liquid chloromethyleneformamidine which collected in the glass tube set to a glass-like solid.

The dimer of hydrocyanic acid, *iminoformyl isocyanide* was prepared in the following manner:

One molecule of chloromethyleneformamidine was heated with one molecular equivalent of quinoline and the vapors were passed with the aid of an air current through a U-tube cooled with solid carbon dioxide. The compound was obtained as a white solid, melting at 85°, in nearly quantitative yield.

The sesquichloride reacts with benzene in the presence of anhydrous aluminum chloride to form the diphenylmethylformamidine halide, $(C_6H_2)_2CH.NH.CH{:}NH.HCl$, a fact which may be advanced in support of the structure assigned to these compounds, $X_2CH.NH.CH{:}NH.HX$, the symbol X representing a halogen atom.

Alad and Skita[7] condensed the sesquichloride with sodium malonic ester to dihydroxy nicotinic acid ester.

The sesquichloride reacts with primary amines to give a substituted formamidine and formamidine:

$$HN{=}CHNHCHCl_2.HCl + RNH_2 \rightarrow HN{=}CHNH.CH{=}NR.HCl + 2HCl$$
$$HN{=}CHNHCH{=}NR + RNH_2 \rightarrow HC({:}NR).NHR + HC({:}NH)NH_2$$

Amidines have thus been made with aniline, *m*- and *p*-nitroaniline, *p*-chloroaniline, *o*-, *m*- and *p*-toluidine, *m*-xylidine, pseuducumidine, α-naphthylamine, β-naphthylamine, *p*-anisidine, *o*-anisidine, *p*-phenetidine, phenylhydrazine, phenylenediamine and benzidine.

Hydrochloric acid reacts at −15° with hydrocyanic acid containing an equivalent of water to form formamide.

Hydrochloric acid reacts with hydrocyanic acid in the presence of quinoline to form iminoformyl cyanide. The transitory formation of iminoformyl chloride probably forms the first stage of the reaction, quinoline serving to abstract hydrochloric acid from two molecules of this compound, causing condensation and the formation of the isocyano grouping,

$$2HCCl{:}NH + 2C_9H_7N \rightarrow HC(.NC){:}NH + 2C_9H_7N.HCl$$

Halogen acids react with iminoformyl isocyanide to form halomethyleneformamidines:

$$HC(NC){:}NH + HCl \rightarrow HN{:}CH.N{:}CH.Cl$$

Cobb and Walton[8] studied the reaction between hydrocyanic acid and *sulfuric acid.* They isolated a compound of the empirical formula, $HCN.H_2SO_4$, which forms by the interaction of the hydrocyanic acid and sulfuric acid at 0°, as a deliquescent, unstable compound insoluble in inert solvents. It is decomposed by water and alcohol. With water, it gives formic acid and ammonium bisulfate

$$HCN.H_2SO_4 + 2H_2O \rightarrow HCOOH + NH_4HSO_4$$

It seems probable that the compound is iminoformyl sulfate, $HC({:}NH).SO_4H$.

The reaction between hydrocyanic acid and sulfuric acid proceeds rapidly. With one mol of hydrocyanic acid and 7 mols of 100% sulfuric acid at 10° the half period, *i.e.*, the time required for the disappearance of half of the hydrocyanic acid, is 27.2 minutes. The presence of water causes a decrease; the presence of excess SO_3 causes some increase in the rate of reaction.

When heated, the sulfuric acid complex decomposes with evolution of sulfur dioxide and carbon dioxide, and, in case an excess of sulfuric acid is present, some carbon monoxide. If a 70 to 90% excess of sulfuric acid is present, there is quantitative formation of carbon monoxide. The rate of hydrolysis is most rapid with acid of 78 to 79% H_2SO_4 content.

Cobb and Walton also studied the reaction between *phosphoric acid* and hydrocyanic acid, and identified a compound of the empirical formula, $HCN.H_3PO_4$. The reaction proceeds at a considerably slower rate with phosphoric acid as compared with sulfuric acid. Thus, in one test, the half period was found to be 36 days.

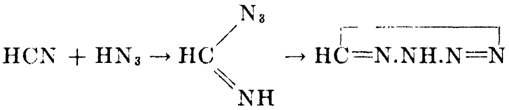
The complex $HCN.H_3PO_4$ is originally a viscous liquid, which crystallizes as a white solid insoluble in most ordinary solvents. It dissolves in water with decomposition. The complex is decomposed on heating, the gaseous product resulting from the decomposition being pure carbon monoxide[8].

Sulfurous acid is without action on hydrocyanic acid, but *acid sulfites* of alkali metals react readily to form a disulfonate:

$$HCN + 2KHSO_3 \rightarrow (KSO_3)_2CH.NH_2$$

Alkali cyanides react with sulfurous acid to form the same compound[9]. The primary potassium salt, $HCN.KHSO_3.H_2SO_3$, is slightly soluble; the secondary salt, $HCN.2KHSO_3.H_2O$ is very soluble.

Hydrocyanic acid reacts with hydrazoic acid forming tetrazole. An imidazole is probably the first product of the reaction:

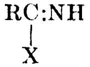


$$HCN + HN_3 \rightarrow HC\begin{array}{l}\diagup N_3\\ \diagdown\!\!\diagdown NH\end{array} \rightarrow \overset{\boxed{}}{HC{=}N.NH.N{=}N}$$

Tetrazole results also through the interaction of hydrazoic acid with cyanogen bromide, cyanoformic esters, isonitriles and fulminic acid.

Reaction of Acids with Nitriles

It has been generally assumed that halogen acids react with nitriles to form imino halides of the type



$$\underset{\displaystyle X}{\underset{|}{RC}}{:}NH$$

Hantzsch[12] has shown that the reaction products of halo acids and nitriles behave in many respects as nitrilium salts RCN:2HX, and that with water they yield the original nitriles. The dihalide is unstable and changes to the more stable monohalide when kept in a desiccator over solid potassium hydroxide.

The compounds may be readily obtained as insoluble crystalline solids by passing vapors of the halogen acid through a solution of the nitrile in ether.

Acetonitrile and *propionitrile* form addition products with one or two molecules of hydrogen chloride; aliphatic nitriles, in general, give addition products with one molecule, though addition compounds with two molecules of hydrogen chloride are also known. *Benzonitrile* combines with two molecules of hydrogen chloride or bromide[10]. Hydrochloric acid at first dissolves in propionitrile, a precipitate appears only on standing for a month or longer. Hydrobromic acid and hydriodic acid react rapidly with acetonitrile and propionitrile[11].

Propionitrile forms a very stable addition product with hydrochloric acid. From this compound propylphenylamidine may be obtained by reaction with aniline in absolute alcohol[13]:

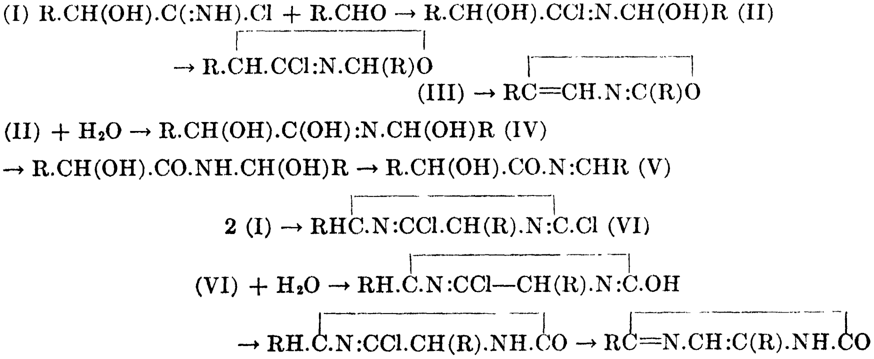
$$CH_3.CH_2.C(:NH).Cl + H_2NC_6H_5 \rightarrow CH_3.CH_2.C(:NH).NHC_6H_5.HCl$$

Engler obtained *hydrobromic acid* addition products from *p*-aminobenzonitrile, acetonitrile, propionitrile and benzonitrile[14].

Biltz[15] prepared the *hydriodic acid* addition products from benzonitrile, *o*-, *m*- and *p*-tolunitriles, *o*-, *m*- and *p*-nitrobenzonitriles, acetonitrile, propionitrile, phenylacetonitrile, terephthalonitrile, cinnamonitrile, triphenylacetonitrile, mandelonitrile and *β*-naphthonitrile.

It is not clear why nitriles, in contrast to other nitrogen compounds, should form salts with two molecules of acid; also amide formation is not simply explained on the basis of Hantzsch's hypothesis. In explanation of amide formation, Hantzach postulated the formation of a hydrinium compound such as RC(OH):NH.HCl, without advancing a reason for this assumption. Perhaps the truth is that the compounds between acids and nitriles are in fact imino-acids in which the acid radical is very loosely attached to the carbon atom.

Aromatic cyanohydrins undergo a complex series of reactions in the presence of hydrochloric acid. Ingham[16] assumed that iminochlorides, RCH(OH).C(:NH).Cl, are formed as intermediates, which undergo a series of changes as follows:



$$\text{(I) } R.CH(OH).C(:NH).Cl + R.CHO \rightarrow R.CH(OH).CCl:N.CH(OH)R \text{ (II)}$$

$$\rightarrow R.CH.CCl:N.CH(R)O \qquad \text{(III)} \rightarrow RC{=}CH.N:C(R)O$$

$$\text{(II)} + H_2O \rightarrow R.CH(OH).C(OH):N.CH(OH)R \text{ (IV)}$$

$$\rightarrow R.CH(OH).CO.NH.CH(OH)R \rightarrow R.CH(OH).CO.N:CHR \text{ (V)}$$

$$2 \text{ (I)} \rightarrow RHC.N:CCl.CH(R).N:C.Cl \text{ (VI)}$$

$$\text{(VI)} + H_2O \rightarrow RH.C.N:CCl{-}CH(R).N:C.OH$$

$$\rightarrow RH.C.N:CCl.CH(R).NH.CO \rightarrow RC{=}N.CH:C(R).NH.CO$$

Mandelonitrile and substituted mandelonitriles also react with hydrochloric acid to form *α*-chloromandelamides:

$$C_6H_5CH(OH).CN + HCl \rightarrow C_6H_5CH(Cl).CONH_2$$

The chlorine in these compounds is very reactive.

The character of the carbon-to-oxygen bond in acylated mandelonitriles is influenced by substituents in the phenyl group. Thus, when the substituents are alkyloxy groups, hydrochloric acid reacts readily with the acetylated compound to form *α*-chloroamides. Acetyl groups attached to the phenyl group decrease the reactivity of the carbon to oxygen bond. The effect becomes more marked as the number of acetoxy groups increases[18].

Acetonitrile is transformed into the hydrochloride of acetamide when it is dissolved in glacial acetic acid containing hydrogen chloride and kept overnight, one equivalent of acetyl chloride forming simultaneously[17]:

$$CH_3.CN + HOCO.CH_3 + 2HCl \rightarrow CH_3CONH_2.HCl + CH_3COCl$$

Propionitrile reacts in a like manner. The reaction is applicable also to hydrogen fluoride.

The acid compounds of nitriles are gradually converted in water to the corresponding amides. Conversion occurs very slowly at ordinary temperature. The rate of amide formation is related to the concentration of the acid; in highly dilute acids, amide formation does not occur. Amide formation is greatly accelerated by heat. Monochloroacetonitrile forms a secondary amide, $(Cl.CH_2CO)_2NH$.

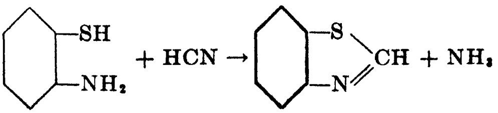
Hahn, Stiehl and Schulz[18] prepared the following:

	m.p. °*C*	*Yield* %
α-Chloro-(3-acetoxy-4-methoxyphenyl)-acetamide	135–6	62
α-Chloro-(3,4-methylenedioxyphenyl)-acetamide	107	
α-Methoxy-(3,4-dimethoxyphenyl)-acetamide	126	53
α-Amino-(3,4-dimethoxyphenyl)-acetamide	132–4	75
α-Diethylamino-(3,4-dimethoxyphenyl)-acetamide	133	74
α-Anilino-(3,4-dimethoxyphenyl)-acetamide	167–9	79
α-Homoveratrylamino-(3,4-dimethoxyphenyl)-acetamide	146	31
α-Azimino-(3,4-dimethoxyphenyl)-acetamide	145	77
α-Azimino-(3-acetoxy-4-methoxyphenyl)-acetamide	124	88
α-Azimino-(3,4-methylenedioxyphenyl)-acetamide	95.5–6.5	85
α-Nitrilo-(3,4-dimethoxyphenyl)-acetamide	151	46.5
N-Phenyl-N′-homoveratrylurea from $3,4(MeO)_2.C_6H_3.CH_2CONH_2$ and PhNCO	166	56

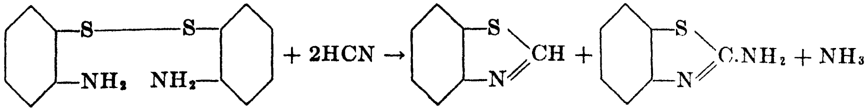
The reaction of sulfuric acid with nitriles proceeds in a rather complicated manner; mono- and disulfonic acids with one carbon atom less than the original nitrile have been identified in the reaction product[34].

Concentrated sulfuric acid reacting with cyanohydrins, $R_1R_2C(OH)CN$, gives amido esters, $R_1R_2C(OSO_3H)CONH_2$. Boiling dilute hydrochloric acid decomposes amido sulfuric esters derived from ketones within about two hours, but causes only a partial hydrolysis of the esters derived from aldehydes after several days[35].

An interesting case of imino compound formation is presented by the reaction of *o*-aminophenylmercaptan with hydrocyanic leading to the formation of benzothiazole[19].



A similar reaction occurs with 2,2-diaminodiphenyl disulfide leading to the formation of benzothiazole and 2-aminobenzothiazole[20]:

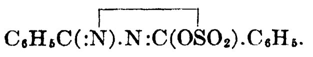


Hantzsch failed to obtained addition products with nitriles and perchloric acid[12].

Reaction with Nitric Acid. Certain aromatic nitriles are readily nitrated with concentrated nitric acid. Benzyl cyanide is nitrated with nitric acid of 1.48 specific gravity at −5°. The nitrile should be added very slowly and with good agitation to the cooled acid[21]. Phenylpropionic nitrile has been nitrated in a similar manner.

Phenylethyl acetonitrile has been nitrated with a one-to-two mixture of nitric and sulfuric acids[22]. *o-Tolunitrile* may be nitrated with nitric acid at 20 to 50° or with a mixture of nitric and sulfuric acids (density = 1.4) at 15 to 20°, to 4-nitro-1-methyl-2-cyanobenzene, $NO_2.C_6H_3(CH_3).CN$, m.p. 106–108°. Nitrated with a mixture of nitric and sulfuric acids of density 1.52, this compound yields 3,5-dinitro-2-methyl-1-cyanobenzene[23]. *p-Tolunitrile* has been nitrated with fuming nitric acid (94%) to 2-nitro-*p*-tolunitrile, m.p. 107–108°, in 85% yield[24].

Reaction with Sulfur Trioxide. Sulfur trioxide reacts with *acetonitrile* forming a yellow hygroscopic powder having the approximate empirical formula, $(CH_3CN)_3.2SO_3$. The compound has not been obtained in a pure form because it is not soluble in indifferent solvents[25]. Sulfur trioxide reacts with *benzonitrile* to form the compound[26]



$$C_6H_5C(:N).N:C(OSO_2).C_6H_5.$$

Tolunitrile gives a similar compound (m.p. 161.5–162°)[27], which on hydrolysis, gives $CH_3C_6H_4C(:NH).NH.CO.C_6H_4CH_3$, and $(CH_3C_6H_4CO)_2NH$. Engelhardt obtained the compound, $NH_2.C_{14}H_5S_2O_8$, by the action of sulfur trioxide on benzonitrile[28].

Eitner[25] prepared acetyl acetamidine sulfonic acid, $CH_3C(:NSO_3).NH.CO.CH_3$, by the action of fuming sulfuric acid containing 28% free SO_3 on acetonitrile, followed by hydrolysis.

Sulfobenzoic acid and benzodisulfonic acids have been obtained by the action of fuming sulfuric acid on benzonitrile[29]. Gumpert[30] prepared dibenzamide, $(C_6H_5CO)_2NH$, by the action of fuming sulfuric acid on benzonitrile.

Reaction with Organic Acids. Nitriles do not react with organic acids at ordinary temperatures at an appreciable rate; reaction takes place upon heating a mixture of nitrile and acid at a comparatively high temperature in a sealed tube. The reaction generally leads to the formation of secondary amides, but an exchange of nitrile and carboxylic groups may also take place. Colby and Dodge, who carried out the first extensive study of the reaction, arrived at the following generalizations:

(1) Fatty nitriles reacting with fatty acids give secondary amides.

(2) Fatty nitriles reacting with aromatic acids exchange their cyano and carboxyl groups giving fatty acids and aromatic nitriles.

(3) Aromatic nitriles and fatty acids give mixed secondary amides.

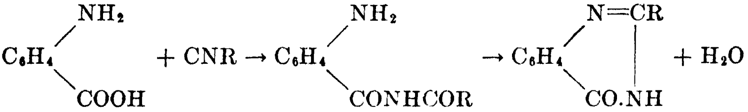
(4) Aromatic nitriles and aromatic acids give mixed secondary amides.

These rules do not hold strictly. Thus, benzoic acid and succinonitrile give succinimide and benzoic acid; succinonitrile and phenylacetic acid give succinimide and phenylacetonitrile; phthalic anhydride and propionitrile give phthalimide; diphenyl-2.2′-dicarboxylic acid and acetonitrile give the imide of the former[38].

Hydrocyanic acid heated with acetic acid in a sealed tube at 200° forms acetamide; under the same conditions *acetonitrile* gives diacetamide $(CH_3CO)_2NH$, m.p. 59°. With propionitrile a compound of the empirical formula, $C_{16}H_{12}N_2O_3$, and propiodiacetamide, $C_{17}H_{14}N_2O_3$, m.p. 68°, are obtained[31].

Glutaronitrile, $CN(CH_2)_3CN$, and acetic acid give glutaramide, and acetonitrile[39].

Anthranilic acid heated under pressure with nitriles gives ketodihydroquinazolines, an acyl amide probably forming as the intermediate product[33]:



$$C_6H_4\begin{cases}NH_2\\COOH\end{cases} + CNR \rightarrow C_6H_4\begin{cases}NH_2\\CONHCOR\end{cases} \rightarrow C_6H_4\begin{cases}N{=}CR\\CO.NH\end{cases} + H_2O$$

Nitriles heated with acid anhydrides form tertriary acid amides:

$$RCN + O(COR')_2 \rightarrow RCO.N(COR')_2$$

Nitriles heated with carboxylic acids in the presence of hydrogen chloride give the corresponding amide[32]:

$$RCN + HOCOR' + HCl \rightarrow RCONH_2 + ClCO.R'$$

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Chapter 4

Aminolysis of Nitriles

Formation of Amidines

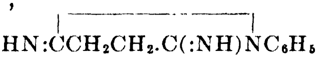
The condensation of ammonia or an amine with a nitrile leads to the formation of an amidine:

$$RCN + H_2NR' \rightarrow RC(NH).NHR'$$

In general, the free amines do not react with nitriles, except in the presence of the hydrochloride of the amine. Thus, benzamidine forms when a mixture of benzonitrile and ammonium chloride is heated with ammonia. Amidines may also be obtained by this method from aromatic amines and nitriles[1]. Diphenylformamidine has been made by this reaction from hydrocyanic acid and aniline:

$$HCN + 2C_6H_5NH_2 + HCl \rightarrow HC(:NC_6H_5).NH.C_6H_5 + NH_4Cl$$

Diphenylbenzamidine has been prepared in poor yield from benzonitrile and diphenylamine[2]. Succinonitrile, heated with aniline hydrochloride at about 180°, gives phenylsuccinimidine[3],



$$HN:CCH_2CH_2.C(:NH)NC_6H_5$$

Salts of amidines are obtained when nitriles are added to a solution of potassium amide in liquid ammonia[4]:

$$RCN + KNH_2 \rightarrow RC(:NH)NHK$$

Amidines containing at least four carbon atoms have been prepared by treating the nitrile with sodium amide in the absence of liquid ammonia at a temperature below the decomposition point of the resulting sodium salt of the amidine. The amidine is obtained by hydrolysis[5].

Aromatic nitriles react with sodium amide to form the sodium salt of the corresponding amidines. Yields are low when the nitrile is heated with sodium amide; better yields are obtained when the reaction is carried out in a liquid diluent such as toluene. Kirssanoff and Poliakowa[6] report the following yields:

Benzamidine from benzonitrile	15–20%
p-Toluamidine from *p*-tolunitrile	60%
β-Naphthoamidine from *β*-naphthonitrile	40–50%

Acetonitrile reacts vigorously in contact with an excess of sodium amide in ether, but the product of the reaction does not contain acetamidine. The nitrile largely polymerizes because the velocity of polymerization is greater than the velocity of formation of the amidine.

Amidines have also been obtained by the condensation of nitriles with amines in presence of metallic sodium, followed by hydrolysis[7]:

$$2C_6H_5CN + C_6H_5NH_2 + 2Na \rightarrow C_6H_5C(:NH)N(Na)C_6H_5 + NaCN + C_6H_6$$
$$C_6H_5C(:NH).N(Na).C_6H_5 + H_2O \rightarrow C_6H_5C(NH).NH.C_6H_5 + NaOH$$

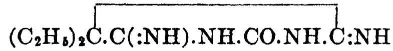
The reaction may be carried out in benzene. It is necessary to heat the mixture for several days under a reflux condenser.

Trichloroacetonitrile, treated with ammonia or primary amines or hydroaromatic amines, gives amidines. With ammonia the reaction takes place in the cold[122].

Aliphatic nitriles react with fused potassium amide to form dipotassium cyanamide and one or more hydrocarbons[8]:

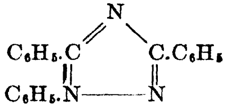
$$RCN + 2KNH_2 \rightarrow K_2CN_2 + NH_3 + RH$$

Diethylmalononitrile combines with urea in the presence of sodium ethoxide forming 2-oxo-4,6-diimino-5,5-diethylhexahydropyrimidine[9],

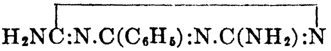


$$(C_2H_5)_2C.C(:NH).NH.CO.NH.C:NH$$

Phenylhydrazine and other aromatic hydrazines condense with nitriles in the presence of metallic sodium to form 1,3,5-substituted triazoles[10]. Thus, phenylhydrazine gives with benzonitrile 1,3,5-triphenyltriazole,



Benzoguanamine or 4,6-diamino-2-phenyl-1,3,5-triazine,

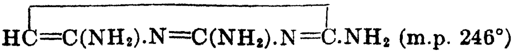


$$H_2NC:N.C(C_6H_5):N.C(NH_2):N$$

results from the reaction of benzonitrile with dicyanodiamide in the presence of piperidine. The compound, which is also known under the name of Benzamin, is the basis of melamine type plastics obtained by condensation with formaldehyde.

Benzamin is prepared on a large scale in Germany in the following manner: A mixture consisting of 363 pounds of benzonitrile, 30 pounds of potassium carbonate and 11 pounds of piperidine is heated to 180–185°, and a suspension of 750 pounds of dicyanodiamide in 1,450 pounds of benzonitrile containing 44 pounds of piperidine in solution, preheated to 90–100°, is introduced in the course of two and one-half hours. The whole is then heated to 185–190° for two hours. The unreacted benzonitrile and the piperidine are recovered by distillation under reduced pressure, and the dry crude Benzamin is removed. It is ground and washed with hot water and finally filtered. The yield of wet cake corresponds to 1,520 pounds of dry Benzamin.

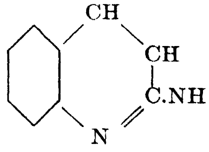
2,4,6-Triaminopyrimidine,



$$HC{=}C(NH_2).N{=}C(NH_2).N{=}C.NH_2 \text{ (m.p. 246°)}$$

has been made through the interaction of malononitrile and guanidine in the presence of sodium ethoxide[116].

o-Aminobenzonitrile condenses under the action of strong alkalies to aminoindole[117]. *o*-Aminocinnamonitrile, $H_2NC_6H_4CH{=}CHCN$, similarly condensed gives α-aminoquinoline[118]



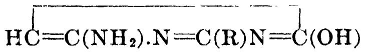
Amidines form readily by the interaction of ammonia or amines with iminoether hydrochlorides:

$$CH_3C(:NH)OC_2H_5.HCl + H_2NR \rightarrow CH_3.C(NH)NHR.HCl + C_2H_5OH$$

Amidines are converted quantitatively to thioamides by treatment with hydrogen sulfide or carbon disulfide, in the case of the latter on heating to 100°:

$$R_1C(:NH)NHR_2 + 2H_2S \rightarrow R_1CSNHR_2 + NH_4HS$$
$$R_1C(:NH)NHR_2 + CS_2 \rightarrow R_1CSNHR_2 + HSCN$$

Amidines, $RC(:NH)NH_2$, react with ethyl cyanoacetate in the presence of sodium ethoxide forming 2-substituted *4-hydroxy-6-aminopyrimidines*[119]



$$HC{=}C(NH_2).N{=}C(R)N{=}C(OH)$$

Formation of Guanidines and Biguanides

The nitrile group in cyanamide and its derivatives undergoes aminolysis in the same manner as the nitrile group in hydrocarbon cyanides; thus, monosubstituted guanidines form by heating together cyanamide and the hydrochloride of an amine:

$$H_2NCN + R.NH_2.HCl \rightarrow H_2NC(NH)NH.R.HCl$$

Guanidine nitrate forms on heating a concentrated aqueous solution of ammonium nitrate with a metallic cyanamide at 90–130°[11]. The reaction also proceeds well with substituted cyanamides which yield substituted guanidines:

$$RNH.CN + C_6H_5NH_2.HCl \rightarrow RNH.C(NH)NH.C_6H_5.HCl$$

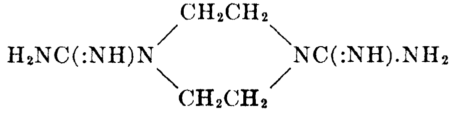
A large number of guanidines have been prepared by this method. Primary amines react readily and secondary amines less readily in this reaction. The presence of strongly electronegative nuclear substituents in an aromatic amine decreases the tendency to form guanidines by reaction with cyanamides.

The reaction proceeds well in the case of *aliphatic amines*. Thus, *iso*amyl-, hexyl-, heptyl-, phenylethyl-guanidines have been prepared from the corresponding amine hydrochlorides and cyanamide. Diguanidines have also been made from *aliphatic diamines* and cyanamide[12]. Mono-substituted guanidines, prepared from cyanamide and aliphatic amine hydrochlorides containing 10 to 16 carbon atoms, have been proposed as bactericides[13].

Good yields of *unsym.* dimethylguanidine are obtained by heating dicyandiamide with *dimethylamine* at 180° for three hours:

$$H_2NC(NH).NH.CN + 2HN(CH_3)_2 \rightarrow 2H_2NC(NH).N(CH_3)_2$$

Monomethylguanidine may be prepared from *methylamine* by the same method[14]. A diguanidine,



has been made from *piperazine hydrochloride* and cyanamide[15].

Methyl-ethanolamine, $CH_3NH.CH_2CH_2OH$, reacting with cyanamide gives the guanidino alcohol[123] $H_2NC(:NH)N(CH_3)CH_2CH_2OH$.

Hydroxylamine hydrochloride, reacting with cyanamide gives the unstable hydroxyguanidine hydrochloride[124] $H_2NC(:NH)NHOH.HCl$.

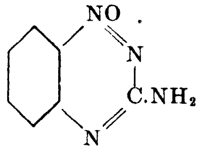
Aralkyl amines react much the same as aliphatic amines. Braun and Randall[16] prepared phenyl benzyl-, dibenzyl- and tribenzyl-guanidines by this method. *Aromatic amine hydrochlorides* also form guanidines readily upon heating with cyanamide or substituted cyanamides. Phenylguanidine hydrochloride is obtained by heating equimolecular quantities of cyanamide and *aniline hydrochloride* in alcoholic solution for four to five hours. The compound crystallizes in needles melting at 128°; the free base melts at 50–60°[17]. Mono-*o*-tolyl-, *p*-tolyl- and cyclohexyl-guanidines have been prepared by this method in yields of 31.6, 17.4 and 64% of theory, respectively[18].

Aromatic acyl cyanamides reacting with hydrochlorides of aromatic monoamines in boiling alcoholic solution give acylated guanidines[102]:

$$RCONHCN + H_2NR'.HCl \rightarrow HNC(NHR').NHCOR.HCl$$

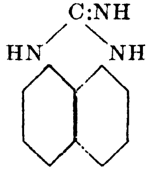
Sym. diphenylguanidine is obtained by heating at 100° the product of reaction of cyanogen chloride with somewhat more than two molecular equivalents of aniline at ordinary temperature. Phenyl cyanamide and aniline hydrochloride are products originally formed upon the interaction of the cyanogen halide and aniline in the cold. Other *sym.* aromatic guanidines may also be prepared by this method. *Unsym.* diphenylguanidine has been obtained in 75% yield by the reaction of cyanamide and *diphenylamine* promoted by hydrochloric acid. β-Naphthylguanidine has been obtained similarly[19]. *Unsym.* triphenylguanidine has been made from *phenyl cyanamide* and *diphenylamine hydrochloride*[20]; *sym.* tetraphenylguanidine has been made from *diphenylamine* and cyanogen chloride, diphenyl cyanamide being first formed in the reaction[21].

o-, m- and p-Nitrophenylguanidines have been obtained from the corresponding nitroanilines[19]. *o*-Nitrophenylguanidine undergoes ring closure on warming a solution of the compound in dilute sodium hydroxide, forming aminophenotriazoxime,



This compound melts at 269° and is difficulty soluble in water[22].

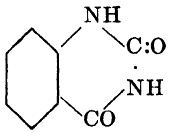
Diguanido-2,7- and diguanido-1,5-naphthalene have been made from the corresponding *naphthalenediamines* and cyanamide. Naphthalene-1,8-diamine gives aminoperimidine[23]:



4,4'-Diguanidodiphenyl, $H_2NC(:NH)NHC_6H_4NHC(:NH)NH_2$, and 4,4'-diguanidodiphenylmethane, $H_2NC(:NH)NHC_6H_4CH_2C_6H_4NHC(:NH)NH_2$ have been prepared from *p-phenylenediamine* and from *p-diaminodiphenylmethane* hydrochlorides and cyanamide[24].

Cyanamide dihydrochloride, reacting with α- and *β-aminoanthraquinones* at 70 to 150° in the presence of excess hydrogen chloride, forms α- and β-guanidoanthroquinones. The α-compound undergoes ring closure forming C-amino-1,9-pyrimidinanthrone, yellow needles, melting at 290 to 295°[25]. The 4-benzoylated product, which may be made from 4-benzoyl-α-aminoanthraquinone and cyanamide dihydrochloride, is a dye.

Cyanogen bromide, reacting with *anthranilic acid* in warm aqueous solution, gives first presumably *o*-carboxyphenyl cyanamide and as the end product di-*o*-carboxyphenylguanidine[26], $(HOCO.C_6H_4NH)_2CNH$. Upon hydrolysis by boiling dilute hydrochloric acid, this compound is converted to benzoyleneurea:



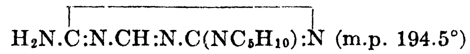
Phenylhydroxy cyanamide, $C_6H_5N(OH)CN$, and diphenylhydroxyguanidine have been made from *phenylhydroxylamine* and cyanogen bromide[27].

Biguanides result from the aminolysis of *dicyanodiamide:*

$$H_2NC(:NH).NH.CN + H_2NR \rightarrow H_2NC(:NH)NH.C(:NH)NHR$$

Cupric sulfate catalyzes the reaction. Biguanide, $H_2NC(NH).NH.C(NH)NH_2$, in the form of the nitrate is obtained by the interaction of dicyanodiamide and ammonium nitrate. Biguanide nitrate upon further reaction with ammonium nitrate gives guanidine nitrate[28].

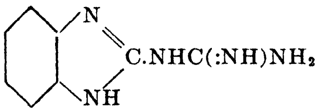
Ethyl-, phenyl-[29]; piperidyl[30]; *o*-, *m*-, *p*-cresyl-, benzyl-[31]; hydroxyphenyl- and methoxyphenyl-biguanides[32] have been made from dicyanodiamide and the hydrochlorides of the appropriate amines. On long standing in chloroform, piperidylbiguanide changes to piperylformoguanamine,



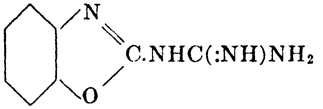
$H_2N.C{:}N.CH{:}N.C(NC_5H_{10}){:}N$ (m.p. 194.5°)

This compound also forms by heating piperidylbiguanide with formic acid at 190–200°[29]. Dicyanodiamide does not react with nitroanilines, though nitrophenylbiguanides have been made by nitrating phenylbiguanide in sulfuric acid. 2-Nitro-, 2,4-dinitro- and trinitrophenylbiguanides have been prepared[113].

Dicyanodiamide reacts with *o*-phenylene diamine to form 2-guanidinobenzimidazole[35],



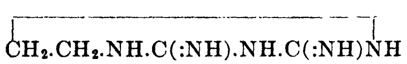
With *o*-aminophenol it gives guanidino benzoxazole[39],



This compound gives a quaternary ammonium compound with methyl iodide.

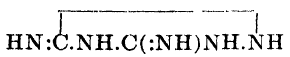
Slotta and Tschesche[33] prepared 1,5-dimethyl- and 1,5-diallylbiguanides by reaction of sodium dicyanodiamide with *methyl-* and *allylamine hydrochlorides*, and 1,1,5,5-tetramethylbiguanide by reaction of copper dicyanodiamide with *dimethylamine hydrochloride.*

Ethylenediamine hydrochloride, heated with dicyanodiamide first at 80–100° then at 140–150°, forms the hydrochloride of ethylenebiguanide[34],



$CH_2.CH_2.NH.C({:}NH).NH.C({:}NH)NH$

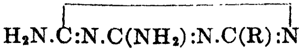
Hydrazine hydrate, heated with dicyanodiamide at 100°–110°, forms guanazole,



$HN{:}C.NH.C({:}NH)NH.NH$

in theoretical yield. Hydrazine salts and free hydrazine give melamazin (pyroguanazole)[36], $C_6H_6N_2$. A number of other compounds are also formed simultaneously[37].

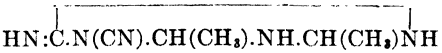
Amidines, $R.C(NH)NH_2$, react with dicyanodiamide forming at first an iminobiguanide, $H_2NC({:}NH).NHC({:}NH)NHC({:}NH).R$, then a diiminotriazine,



$H_2N.C{:}N.C(NH_2){:}N.C(R){:}N$

Compounds of this type have also been obtained by the direct condensation of nitriles RCN with dicyanodiamide. The methyl-, phenyl-, *m*- and *p*-tolyl- and benzyl-derivatives have been made by the reaction of the corresponding nitriles with dicyanodiamide. *Iso*valero-, *iso*capro- and *o*-tolyl-nitriles do not form triazines[38].

Dicyanodiamide condenses with *aldehyde ammonia* to iminodimethyl-N-cyanohexahydrotriazine,



$$HN{:}C.N(CN).CH(CH_3).NH.CH(CH_3)NH$$

Formation of Amidoximes

Hydroxylamine reacts with nitriles to form amidoximes:

$$RCN + H_2NOH \rightarrow RC(:NOH)NH_2$$

As a rule the reaction takes place slowly but in the case of certain types of nitriles, such as chlorinated acetonitriles, it takes place quite readily. The reaction proceeds well in the case of nitriles, $C_nH_{2n+1}CN$, if n is 5 or less, or lies between 10 and 13 inclusive; but slowly in the case of nitriles with 7 to 9 C atoms.

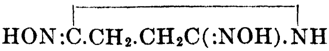
Formamidoxime (Isuret), $H_2NCH{:}NOH$, m.p. 114–115° (dec.), is obtained by allowing an alcoholic solution of hydroxylamine and hydrocyanic acid to stand at ordinary temperature for 48 hours, then evaporating the solution down at 40°[40].

Acetamidoxime, $CH_3C(NOH)NH_2$, m.p. 135° (dec.), is obtained by warming an aqueous-alcoholic solution of equimolecular quantities of acetonitrile and hydroxylamine at 30 to 40° for 60 to 80 hours. The solution should be concentrated under vacuum to avoid decomposition. The compound is best purified as the hydrochloride by precipitation from its alcoholic solution by the addition of ether[41].

Amidoximes have also been prepared from propionitrile[42]; capronitrile[43]; *n*-heptylic nitrile[44]; lauronitrile, myristonitrile, palmitonitrile and stearonitrile[45]. Trichloroacetamidoxime[46], $Cl_3C.C(NOH)NH_2$, m.p. 128–129° (dec.), and tribromoacetamidoxime[47], m.p. 126°, have been made from the corresponding halogenated nitriles. The reaction between these nitriles and hydroxylamine takes place readily, and is carried out in a strongly cooled solution. Tribromoacetamidoxime decomposes in the course of a few days.

Reacting with an ice-cold aqueous solution of hydroxylamine, *cyanogen* forms oxalamidoxime, $H_2NC(:NOH)C(:NOH)NH_2$, in 40% yield[48]. Conducted into an aniline solution of hydroxylamine hydrochloride, cyanogen forms oxalamidoxime and oxalene aniline amidoxime[49], $H_2NC(:NOH)C(:NOH)NHC_6H_5$.

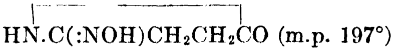
Malonic monoamidoxime[50] (carboxyethenylamidoxime), $HOCOCH_2C(:NOH)NH_2$, forms through the interaction of *cyanoacetic acid* and hydroxylamine at 40°. Cyanoacetamidoxime, $CNCH_2C(:NOH)NH_2$, m.p. 124–127° (dec.), is obtained by the reaction of *malononitrile* with a molecular equivalent of free hydroxylamine in aqueous alcoholic solution. Malonic-bis-amidoxime[51], $H_2NC(:NOH)CH_2C(:NOH)NH_2$, m.p. 163–167° (dec.), results from the reaction of malononitrile with two molecular equivalents of free hydroxylamine in aqueous alcoholic solution. Succinic-bis-amidoxime, $H_2NC(:NOH)CH_2CH_2C(:NOH)NH_2$, m.p. 188° (dec.), forms by the interaction of *succinonitrile* with two molecules of hydroxylamine in alcoholic solution at room temperature[52]. At higher temperatures, the imidoxime,



$$HON{:}C.CH_2.CH_2C({:}NOH).NH$$

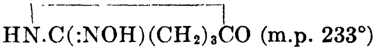
forms.

Hydroxylamine hydrochloride, reacting with succinonitrile, gives succinimidoxime,



$$HN.C({:}NOH)CH_2CH_2CO \text{ (m.p. 197°)}$$

soluble in water, slightly soluble in hot alcohol, insoluble in ether and benzol. Disuccinimidodihydroxamic acid, $HONH.CO.CH_2.CH_2CONH.COCH_2CH_2CONHOH$, m.p. 171°, has been obtained by the interaction of succinonitrile with free hydroxylamine[52,53,54]. Glutaric acid-bis-amidoxime, $H_2NC({:}NOH)(CH_2)_3C({:}NOH)NH_2$, m.p. 233°, forms by the interaction of *glutaric nitrile* with two molecules of hydroxylamine in dilute alcoholic solution at 60 to 70° for 10 hours[54]. Glutarimidoxime, m.p. 196° and glutareneimidoxime,



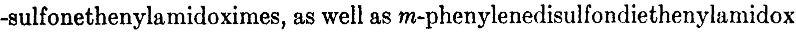
$$HN.C({:}NOH)(CH_2)_3CO \text{ (m.p. 233°)}$$

have also been made by the interaction of glutaronitrile with free hydroxylamine[53].

Ethyl cyanoacetate, reacting with hydroxylamine hydrate in alcohol solution, forms methenylamidoximeacetohydroxamic acid[55]:

$$CN.CH_2COOC_2H_5 + 2H_2NOH \rightarrow H_2NC({:}NOH).CH_2CONHOH + C_2H_5OH$$

Propionylpropionitrile reacts with hydroxylamine to form amidomethyl-*iso*xazole[56]:



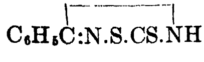
$$C_2H_5CO.CH(CN)CH_3 + H_2NOH \rightarrow C_2H_5C{:}N.O.C(NH_2){:}C.CH_3 + H_2O$$

Aryl sulfonacetonitriles react with hydroxylamine to form amidoximes. The reaction has been carried out in boiling alcoholic solution with two molecular equivalents of free hydroxylamine, heating for a day on the water bath.

Phenyl-, *o*- and *p*-tolyl-, 1,3,4-*m*-xylyl-, ψ-cumyl-, α- and β-naphthyl-, *p*-chloro-*o*-phenyl-, *p*-bromophenyl-, *p*-iodophenyl-, *o*- and *p*-anisol and *p*-phenetol-sulfonethenylamidoximes, as well as *m*-phenylenedisulfondiethenylamidoxime, have been prepared[57].

Benzamidoxime, $C_6H_5C({:}NOH)NH_2$, m.p. 79–80°, forms on heating an aqueous-alcoholic solution of hydroxylamine and benzonitrile at 60 to 80°[58]. The aqueous solution of this compound reacts neutral. It is soluble in alkalies and acids.

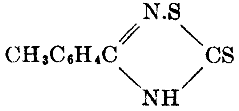
Benzamidoxime reacts with cyanogen in alcohol-benzol solution to form benzamidoxime dicyanide[59], $C_6H_5C({:}NOH)NH.C({:}NH).CN$. It reacts with an excess of carbon disulfide forming benzamidesulfim-N-dithiocarboxylic acid benzamidesulfim[60], $C_6H_5C(NCS.SH)NH.SH.C_6H_5C({:}NH)NHSH$, m.p. 134–136°, slightly soluble in water and alcohol, insoluble in ether. Heated with carbon disulfide and alcoholic potassium hydroxide, benzamidoxime gives 3-phenyl-1,2,4-thiodiazolthion (5)[61],



$$C_6H_5C{:}N.S.CS.NH$$

Nitrobenzamidoximes[62], *o-aminobenzamidoxime*[63] and *o*- and *p-toluic acid amidoximes*[64] have also been prepared. *p*-Toluic acid amidoxime is obtained by heating *p*-tolunitrile and aqueous-alcoholic hydroxylamine at 80 to 90° for 6 hours. The compound melts at 145–146°, and is soluble in alcohol, ether, chloroform and hot water.

When heated with carbon disulfide in alcoholic solution, *p*-toluic acid amidoxime forms amidsulfim-N-dithiocarboxylic *p*-toluamidsulfim[65], $CH_3C_6H_4.C(NH.SH)NCS.SH.CH_3C_6H_4C(NHSH){:}NH$, a very unstable compound. Heated with carbon disulfide in alcoholic potassium hydroxide, the amidoxime gives[66]:



Unsymmetrical m-xylylcarboxyamidoxime, 2,4-$(CH_3)_2C_6H_3C({:}NOH)NH_2$, m.p. 178°, forms on heating *unsym. m*-xylyl cyanide with hydroxylamine at 80 to 85°[67].

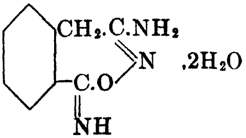
Phenacetamidoxime, $C_6H_5CH_2C(NOH)NH_2$, m.p. 67°, has been prepared by warming an aqueous-alcoholic solution of benzyl cyanide with a molecular equivalent of hydroxylamine to 40 to 50° for 36 to 48 hours in a closed vessel, the solution being then concentrated at a temperature not in excess of 50°[68]. *Phenylnitroacetamidoxime*, $C_6H_5CH(NO_2)C({:}NOH)NH_2$, m.p. 125°, is obtained through the interaction of the sodium compound of phenylnitroacetonitrile and hydroxylamine hydrochloride in water[69]. *Cinnamic amidoxime*, $C_6H_5CH{:}CH.C({:}NOH)NH_2$, m.p. 93°, is obtained by digesting cinnamonitrile and hydroxylamine in aqueous alcoholic solution at 60 to 70° for a few days[70].

α-Naphthamidoxime, $C_{10}H_9C({:}NOH)NH_2$, m.p. 148–149°, forms by the interaction of α-naphthonitrile with hydroxylamine in alcoholic solution. β-Naphthamidoxime, m.p. 150°, similarly forms from β-naphthonitrile and hydroxylamine[77].

Isophthalic monoamidoxime, (1)$HOCO.C_6H_4C({:}NOH)NH_2$(3), m.p. 198°, forms when *m*-cyanobenzoic acid is heated with a molecular equivalent of hydroxylamine at 80 to 100° for twelve hours[72]. *Iso*phthalic-bis-amidoxime, $H_2NC({:}NOH).C_6H_4.C({:}NOH)NH_2$, m.p. 193° (dec.), is obtained by heating isophthalodinitrile with two molecular equivalents of hydroxylamine in alcohol solution[73]. *Homoterephthalic amidoxime (4)-nitrile(1)*, $CN.C_6H_4CH_2C({:}NOH)NH_2$, m.p. 168°, is obtained from homoterephthalic dinitrile and one molecular equivalent of hydroxylamine. The bis-amidoxime, $H_2NC({:}NOH).C_6H_4.CH_2C({:}NOH)NH_2$, m.p. 192° (dec.), forms on heating homoterephthalic dinitrile with three molecular equivalents of hydroxylamine in alcoholic solution for several hours[74].

β-Naphthoamidoxime, $C_{10}H_9C({:}NOH)NH_2$, and *p-quinolylmethyleneamidoxime*, $C_9H_6NC(NOH)NH_2$, have been made from the corresponding nitriles[76]. 3-Cyanopyridine, treated with a concentrated aqueous solution of free hydroxylamine at 70°, forms *nicotinic acid amidoxime*[77], m.p. 128°.

o-Cyanobenzyl cyanide, reacting with hydroxylamine, forms homo-*ortho*-phthalene aminoimidoxime,



The compound loses its water of crystallization between 100 and 110°. The anhydrous compound melts at 158°[75].

When *cinnamic aldehyde cyanohydrin* is heated with a molecular equivalent of hydroxylamine for a few hours on the water bath, it decomposes giving cinnamic aldehyde; the latter reacting with hydroxylamine forms cinnamaldoxime. When the reaction is carried out at 7°, phenyl vinylhydroxethenylamidoxime, $C_6H_5CH{:}CHCH(OH).C({:}NOH)NH_2$, forms[78].

Phenylhydroxylamine, reacting with *cyanogen* in a cold ethereal solution, forms dicyanophenylhydroxylamine, $C_6H_5N(OH).C({:}NH)CN$, m.p. 136° (dec.), in 75% yield[79].

Reaction of Nitriles with Hydrazine and Substituted Hydrazines

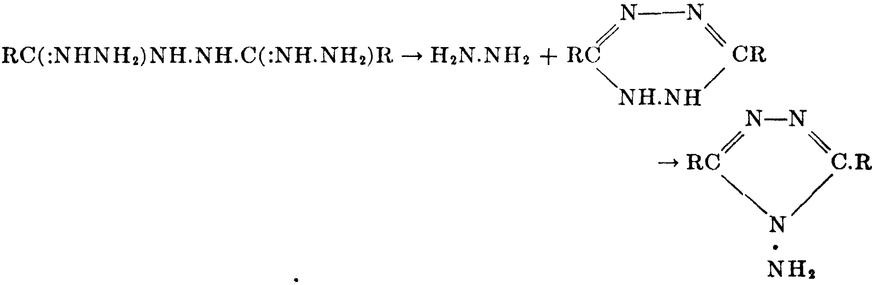
Nitriles react when heated with hydrazine hydrate, probably forming at first a hydrazidine:

$$RCN + H_2NNH_2 \rightarrow RC({:}NH)NH.NH_2$$

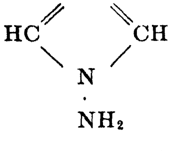
At the temperature at which the reaction rate is appreciable, two molecules of the hydrazidine combine[80]:

$$2RC({:}NH)NHNH_2 \rightarrow RC({:}NH)NH.NH.C({:}NH)R + H_2NNH_2$$
$$2RC({:}NH)NH.NH_2 + H_2N.NH_2 \rightarrow RC({:}N.NH_2)NH.NH.C({:}N.NH_2)R + 2NH_3$$

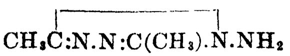
The second compound may condense to a ring, forming an N-aminotriazol:



Hydrocyanic acid reacts with anhydrous hydrazine forming a snow-white, crystalline compound, CNN_2H_5, which decomposes rapidly. When this is heated to 55°, a light yellow oil forms which solidifies under vacuum. This compound is probably $H_2NN{:}CHNH.NHC{:}NNH_2$. When heated until the evolution of ammonia ceases, it forms N-aminotriazole,

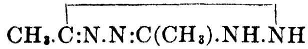


Acetonitrile, heated to boiling with hydrazine hydrate reacts to form principally dimethyl-N-aminotriazol,



$$CH_3C{:}N.N{:}C(CH_3).N.NH_2$$

and some dimethyldihydrotetrazine,



$$CH_3.C{:}N.N{:}C(CH_3).NH.NH$$

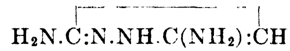
Heated with anhydrous hydrazine for several days, acetonitrile forms exclusively dimethyldihydrotetrazine. *Propionitrile*, on several days' heating with hydrazine, forms in the main diethyl-N-aminotriazol, and a small quantity of diethyldihydrotetrazine; *n-butyronitrile* forms only a trace of dihydrotetrazine; *isovaleronitrile* does not react.

Benzonitrile, heated for several days with anhydrous hydrazine, forms exclusively diphenyldihydrotetrazine. Reacting with a cold alcoholic solution of hydrazine hydrate, benzonitrile forms diphenyldihydrotetrazine and diphenyltetrazine. *o-Tolunitrile* does not react with anhydrous hydrazine; *p-tolunitrile* reacts after several days' heating to form di-*p*-tolyl-dihydrotetrazine; *m-tolunitrile* reacts very readily with anhydrous hydrazine forming di-*m*-tolyldihydrotetrazine.

Benzyl cyanide reacts with anhydrous hydrazine on several days' refluxing to form dibenzylaminotriazole.

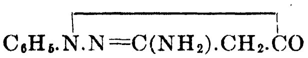
β-Naphthonitrile reacts with anhydrous hydrazine forming di-*β*-naphthyldihydrotetrazine[81].

Malononitrile condenses readily with hydrazine hydrate forming 3,5-diaminopyrazole,



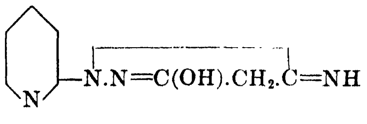
$$H_2N.C{:}N.NH.C(NH_2){:}CH$$

a brown oil which is difficult to purify. *Ethyl cyanoacetate* in alcoholic solution reacts with hydrazine hydrate forming cyanoacethydrazide, $CNCH_2CONH.NH_2$ In aqueous solution both the hydrazide and the hydrazidine, $CH_2(COOC_2H_5)$-$C({:}NH)NH.NH_2$, are formed, the latter undergoing further transformation, ultimately forming a dihydrotetrazine[82]. Reacting with *phenylhydrazine* in the presence of sodium ethoxide, ethyl cyanoacetate gives 1-phenyl-3-amino-5-pyrazolone[114],



$$C_6H_5.N.N{=}C(NH_2).CH_2.CO$$

m-Tolyl-, *m*-chlorophenyl-, *p*-methoxyphenyl-, *p*-sulfamylphenyl-, 3-pyridyl- and 4-pyridyl-hydrazines also give the corresponding 1-substituted 3-amino-5- pyrazolones. 2-Pyridylhydrazine gives under the same conditions 1-(2-pyridyl)-3-hydroxy-5-pyrazoloneimide,



2-Quinolyl- and 2-benzothiazolylhydrazines also give the corresponding 1-substituted 3-hydroxy-5-pyrazoloneimides[115].

Cyanogen reacts in the cold with hydrazine in aqueous solution forming oxalhydrazidine (carbohydrazimine)[83]:

$$2H_2NNH_2 + CN.CN \rightarrow H_2NNHC({:}NH).C({:}NH).NH.NH_2$$

Nitrous acid reacts with the compound giving bis-tetrazole:

$$H_2N.NH.C(NH).C(NH).NH.NH_2 + 2HONO \rightarrow HN.N{:}N.N{:}C.C{:}N.N{:}N.NH + 4H_2O$$

The metal salts of this compound are very explosive; the compound itself explodes on heating to its melting point. Oxalhydrazidine, heated with a large excess of formic acid under a reflux condenser, gives N-formyl-bis-triazole which on hydrolysis with hydrochloric acid forms bis-triazole, m.p. 300°[84],

$$H_2N.NHC(NH).C(NH)NH.NH_2 + 2HCOOH \rightarrow HN.CH{:}N.N{:}C.C{:}N.N{:}CH.NH + 4H_2O$$

Benzonitrile reacts with *phenylhydrazine* in benzol solution in the presence of some sodium compound of phenylhydrazine forming C-diphenyl-N-phenyl-1,2,3-triazole,

$$C_6H_5C{:}N.C(C_6H_5){:}N.N.C_6H_5$$

Dibenzenylphenylhydrazidine, $C_6H_5C({:}NH).N(C_6H_5).NH.C({:}NH)C_6H_5$, probably forms as an intermediate. 1-Phenyl-C-di-orthotolyl-, 1-phenyl-C-diparatolyl-, 1-phenyl-C-di-α-naphthyl- and 1-phenyl-C-di-β-naphthyl triazols have also been made by the same reaction from *o*- and *p*-tolunitriles, α- and β-naphthonitriles and phenylhydrazine. Aliphatic nitriles do not form triazoles but give unstable compounds[85].

Methylpropionylacetonitrile, reacting with phenylhydrazine, forms a pseudo-hydrazide:

$$C_2H_5COCH(CN).CH_3 + H_2NNHC_6H_5 \rightarrow C_6H_5NHN{:}C(C_2H_5).CH(CN)CH_3 \rightarrow C_6H_5.N.N{:}C(C_2H_5).C(CH_3){:}C.NH_2$$

Secondary β-ketonitriles in general, reacting with phenylhydrazine, give amino-pyrazoles,

$$C_6H_5N.N{:}C(R).C(R'){:}C.NH_2$$

while *tertiary β-ketonitriles* form true hydrazides, $C_6H_5NH.N{:}C(R).C(R',R'')CN$. The aminopyrazoles may be converted to pyrazoles,

$$C_6H_5.N.N{:}C(R).C(R'){:}CH$$

by diazotization followed by heating at 100 to 110°[86].

Cyanogen, reacting with a molecule of phenylhydrazine, forms dicyano-phenylhydrazine, $C_6H_5NH.N{:}C(NH_2)CN$, (dec. at 160°)[87]. This compound condenses with aromatic aldehydes, and the condensation products may be converted to phenyl aryl cyanotriazoles,

$$N.C(CN){:}N.C(R){:}N.C_6H_5.$$

by mild oxidation[88]. Reacting with two molecules of phenylhydrazine, cyanogen forms dicyanodiphenylhydrazine[89], $C_6H_5NHN{:}C(NH_2).C(NH_2){:}N.NHC_6H_5$, m.p. 225–226°.

Substituted phenylhydrazines, $C_6H_5N(R).NH_2$, react with nitriles, R′CN, forming N-substituted hydrazidines, $C_6H_5N(R).NH.C({:}NH)R'$. Engelhardt prepared the following representatives: phenylmethylbenzenylhydrazidine, $C_6H_5N(CH_3)NH.C(NH).C_6H_5$, m.p. 105°; phenylethylbenzenylhydrazidine, $C_6H_5N(C_2H_5)NH.C(NH)C_6H_5$, m.p. 105°; diphenylbenzenylhydrazidine, $(C_6H_5)_2N.NH.C(NH)C_6H_5$, m.p. 170°. Hydrazobenzene, $C_6H_5NH.NHC_6H_5$, does not react in this manner[85].

Semicarbazide, $H_2NCONH.NH_2$, reacts with *cyanogen*, forming the compound[90], $H_2NCONH.N{:}C(NH_2).CN$.

Aminoguanidine reacts with cyanogen in alcoholic solution forming the compound, $H_2NC({:}NH).NHNC(NH_2).C(NH_2){:}NNHC({:}NH)NH_2$, m.p. 223° (dec.). This is hydrolyzed with acids to cyanosemicarbazide[91], $H_2N.CO.NH.N{:}C(NH)_2.C(NH_2){:}N.NHCO.NH_2$.

Miscellaneous Reactions

Aromatic amines in alcoholic solution react with cyanogen forming symmetrical diaryl oxaldiamidines; thus, with aniline *sym.*-diphenyloxalamidine, m.p. 210–220°, is obtained[92]:

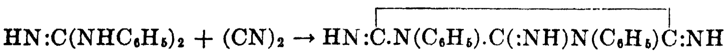
$$C_6H_5NH_2 + (CN)_2 \rightarrow C_6H_5NHC({:}NH).C({:}NH)NHC_6H_5$$

Aliphatic amines do not react with cyanogen.

Cyanogen reacts with ammonia in the absence of water forming hydrazulmine,

$$2(CN)_2 + 2NH_3 \rightarrow C_4H_6N_6$$

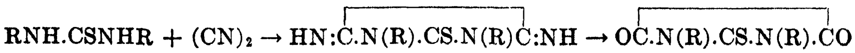
This compound is hydrolyzed with water to azulminic acid, $C_4H_5N_5O$. If the reaction of cyanogen and ammonia is carried out in aqueous solution, then in addition to azulminic acid, oxamide and ammonium oxalate are formed[93]. Cyanogen reacts with diphenylguanidine in cold alcoholic solution forming diphenylparabanic acid triimide:



$$HN{:}C(NHC_6H_5)_2 + (CN)_2 \rightarrow HN{:}C.N(C_6H_5).C({:}NH)N(C_6H_5)C{:}NH$$

Ditolyl-, triphenyl- and tritolylguanidines react in the same manner[94].

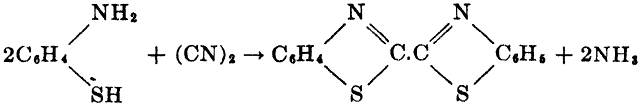
Thioparabanic acid derivatives form when gaseous cyanogen is passed through an alcoholic solution of a thiourea and the resulting diimide is hydrolyzed with hydrochloric acid:



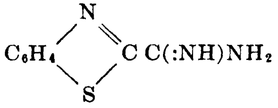
$$RNH.CSNHR + (CN)_2 \rightarrow HN{:}C.N(R).CS.N(R)C{:}NH \rightarrow OC.N(R).CS.N(R).CO$$

The isoamyl- and *p*-tolyl-, phenyl- and dimethyl-thioparabanic acids have been made by this reaction[95].

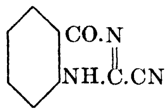
Cyanogen gas passed through an alcoholic solution of *o*-aminophenylmercaptan reacts to form dibenzothiazole:



One molecular equivalent of the aminomercaptan added gradually to a concentrated alcoholic solution of cyanogen reacts to form benzothiazolecarboxylic amidine[96],



Cyanogen reacts with anthranilic acid in aqueous solution forming dicyanaminobenzoyl,



There is also formed some aminobenzoic percyanide, $HOCO.C_6H_4.NH_2(CN)_2$. In alcoholic solution, the reaction products are aminobenzoic percyanide; carbimino-bis-aminobenzoic acid, $HOCO.C_6H_4NHC(:NH).NHC_6H_4COOH$; and ethoxycarbiminoaminobenzoic acid, $HOCO.C_6H_4NH.C(NH).OC_2H_5$. *m*-Aminobenzoic acid reacts with cyanogen in aqueous solution forming *m*-cyanocarbiminoaminobenzoic acid[97], $[HOCOC_6H_4NHC(:NH)CN]_3.H_2O$.

Cyanogen reacts with hydrazoic acid in aqueous solution forming cynaotetrazole, m.p. 99°, and bis-tetrazole, m.p. 254–255°:

$$HN_3 + (CN)_2 \rightarrow HN.N:N.N:C.CN$$

$$2HN_3 + (CN)_2 \rightarrow HN.N:N.N:C.C:N.N:N.NH$$

Hydrolyzed with alkalies, the cyano-compound gives tetrazole, the intermediate carboxylic acid being unstable. Bis-tetrazole forms insoluble heavy metal salts; the silver salt is highly explosive[98].

Cyanogen reacts with diazomethane in ether solution forming cyanosotriazole, m.p. 114°:

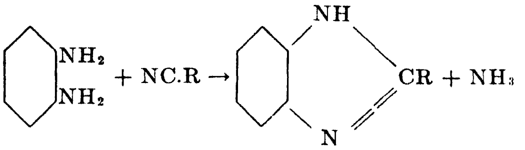
$$H_2CN_2 + (CN)_2 \rightarrow HC:N.NH.N:C.CN$$

A portion of the compound is methylated by further reaction with diazomethane:

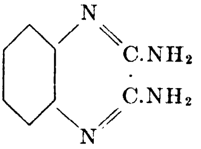
$$HC:N.NH.N:C.CN + H_2CN_2 \rightarrow HC:N.N(CH_3).N:C.CN + N_2$$

Methylation may be prevented by using a very dilute solution of diazomethane (1:800), a large excess of cyanogen and carrying out the reaction at −10°. Diazoethane reacts in the same manner as diazomethane[99].

Nitriles, RCN, heated in an acid medium react with *o*-phenylenediamine hydrochloride to give substituted benzimidazoles:



Cyanogen reacting with *o*-phenylenediamine gives diaminoquinoxaline,

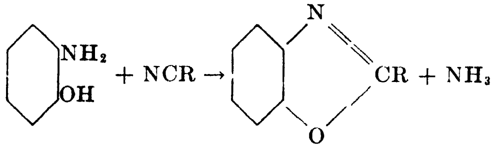


which is hydrolyzed by dilute hydrochloric acid to dihydroxyquinoxaline[120].

Hölljes and Wagner[100] prepared the following imidazoles in the yields indicated:

	M.P., °*C*	*Yield, % of Theory*
Benzimidazole	170.5	5.9
2-Methylbenzimidazole	173.6	27.3
2-Ethylbenzimidazole	172	58.8
2-*n*-Propylbenzimidazole	157–159	71.0
2-*n*-Butylbenzimidazole	150	47.4
2-*n*-Amylbenzimidazole	162	50.0
2-Phenylbenzimidazole	287–288	72.4
2-*p*-Tolylbenzimidazole	266–269	70.9

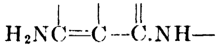
A 74% yield of 2-phenylbenzimidazole was obtained in two hours at 200° when a molecular equivalent of acid was used. Nitriles heated in acid medium with *o*-aminophenol give substituted benzoxazoles[101]:



Hölljes and Wagner[100] prepared the following oxazoles in the yields indicated:

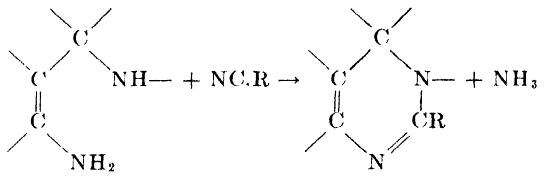
	Boiling Point		*Yield, % of Theory*
	°*C*	*Under mm Hg*	
2-Methylbenzoxazole	59–60	12	33.5
2-Ethylbenzoxazole	75–76	2	61.2
2-*n*-Butylbenzoxazole	68–70	20	49.7
2-*n*-Amylbenzoxazole	114–114.5	2	52.6
2-Phenylbenzoxazole	....	..	70.5
2-*p*-Tolylbenzoxazole	....	..	72.0

A 72% yield of 2-phenylbenzoxazole was obtained on heating a mixture of o-aminophenol hydrochloride and benzonitrile at 200° in the presence of hydrochloric acid for two hours. Furonitrile and 2,6-dimethoxybenzonitrile do not react. Pyrimidines are obtained through the interaction of nitriles with the group,

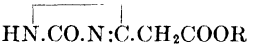


$$H_2NC{=}C{-}C.NH{-}$$

on heating in acid medium:

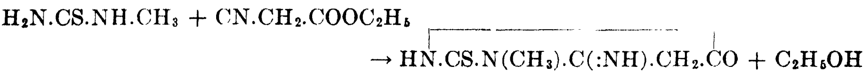


Molten urea heated with methyl- or ethyl cyanoacetate gives a compound of acid character which probably has the structure:



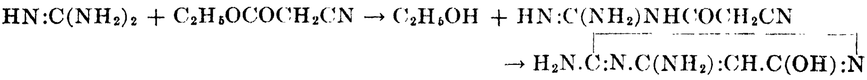
$$HN.CO.N{:}C.CH_2COOR$$

The methyl compound, which crystallizes with one and a half molecules of water, melts at 116°; the ethyl compound melts at 162° with decomposition[103]. Ethyl diethylcyanoacetate reacts with urea at ordinary temperature in the presence of sodium ethylate forming diethylcyanoacetylurea, $(C_2H_5)_2C(CN)CONH.CONH_2$, colorless prisms, melting at 118°. The dipropyl-, dibenzyl-analogs of this compound, as well as diethylcyanoacetylmethyl urea, m.p. 153°, and diethylcyanoacetylphenylurea, m.p. 156°, have also been prepared[104]. Methylthiourea condenses with ethyl cyanoacetate in alcoholic solution in the presence of sodium ethoxide, forming methyl-3-amino-4-oxy-6-thio-3-pyrimidine[105]:



$$H_2N.CS.NH.CH_3 + CN.CH_2.COOC_2H_5 \rightarrow HN.CS.N(CH_3).C({:}NH).CH_2.CO + C_2H_5OH$$

Guanidine reacts with ethyl cyanoacetate as follows[106]:

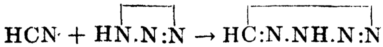


$$HN{:}C(NH_2)_2 + C_2H_5OCOCH_2CN \rightarrow C_2H_5OH + HN{:}C(NH_2)NHCOCH_2CN \rightarrow H_2N.C{:}N.C(NH_2){:}CH.C(OH){:}N$$

Benzonitrile reacts with thiobenzamide[107], forming $C_6H_5C(SH){:}N.C({:}NH)$-C_6H_5.

Benzonitrile reacts with aniline and sulfur forming thiocarbanilide, $(C_6H_5NH)_2$-CS; tolunitrile reacts similarly[108].

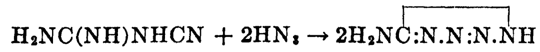
Hydrocyanic acid reacts with hydrazoic acid in alcoholic solution at 100° to form tetrazole:



$$HCN + HN.N{:}N \rightarrow HC{:}N.NH.N{:}N$$

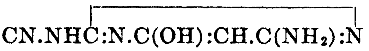
This reaction proceeds very slowly, requiring two to three days for its completion[109]. Tetrazole also forms on heating an aqueous solution of ammonium cyanide at 70–80° for seventy-two hours[110].

Hydrazoic acid reacts with dicyanodiamide forming aminotetrazole[111]:



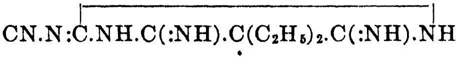
$$H_2NC(NH)NHCN + 2HN_3 \rightarrow 2H_2NC{:}N.N{:}N.NH$$

Dicyanodiamide condenses with ethyl cyanoacetate in the presence of sodium ethoxide to



$$CN.NHC{:}N.C(OH){:}CH.C(NH_2){:}N$$

Diethylmalononitrile, $C_2H_5C(CN)_2$, forms[112]



$$CN.N{:}C.NH.C({:}NH).C(C_2H_5)_2.C({:}NH).NH$$

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Chapter 5

Simultaneous Action of Alcohols and Acids on Nitriles

Iminoethers

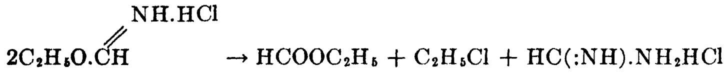
Formation of Iminoethers. Alcohols or other hydroxy compounds reacting in an anhydrous medium with hydrocyanic acid and nitriles in general, in the presence of hydrochloric acid, form salts of iminoethers[1]:*

$$R.CN + HOR' + HCl \rightarrow RC(:NH)OR'.HCl$$

The hydrochlorides of iminoethers are crystalline bodies, which, on heating, generally decompose into an alkyl chloride and an acid amide:

$$C_2H_5O.C(CH_3):NH.HCl \rightarrow CH_3.CONH_2 + C_2H_5Cl$$

Formimino ethyl ether hydrochloride decomposes on heating into formamidine hydrochloride, ethyl formate and ethyl chloride:



$$2C_2H_5O.\overset{\text{NH.HCl}}{\overset{/\!/}{C}}H \rightarrow HCOOC_2H_5 + C_2H_5Cl + HC(:NH).NH_2HCl$$

Pinner prepared free iminoethers by adding the powdered iminoether hydrochloride to an excess of 33% solution of potassium carbonate under good cooling and with vigorous agitation; he extracted the oil which formed with ether, drying the extract with calcium chloride and finally evaporating off the ether. The free ethers may also be prepared by treating the hydrochloride with solid sodium- or potassium hydroxide.

The free iminoethers are liquids or low melting solids. They have an alkaloid-like odor, are insoluble or slightly soluble in water, and are not decomposed by water at ordinary temperature. Iminoethers of low molecular weight may be distilled in part without decomposition; iminoethers of higher molecular weight, especially those derived from aromatic nitriles, decompose into the original nitrile and the alcohol. The free iminoethers are not stable and gradually decompose, probably to the original nitrile and alcohol.

In aqueous solution and in the presence of acids, salts of iminoethers are hydrolyzed to an ester and ammonia. The reaction has been studied by Stieglitz and Cloke and their coworkers[55]. In the presence of bases the salts of iminoethers tend to decompose into the nitrile and the alcohol (or phenol).

Iminoether hydrochlorides derived from aromatic nitriles decompose on heating into a phenol and hydrochloric acid.

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* Iminoethers are also formed from nitriles and alcohol in the presence of sodium ethoxide. The reaction is reversible[44].

The simple free iminoethers decompose on heating into the nitrile and alcohol

$$CH_3C(:NH)OC_2H_5 \rightarrow CH_3CH + C_2H_5OH$$

Benzimino methyl ether decomposes in this manner when heated in a sealed tube at 270–280°:

$$C_6H_5C(:NH)OCH_3 \rightarrow C_6H_5CN + CH_3OH$$

a small amount of cyaphenin forming simultaneously[2].

When hydrocyanic acid is added to an alcoholic solution of hydrogen chloride reaction proceeds with explosive violence, and a number of products are formed. Ethyl formate, diethoxyacetamide, and the acetal of ethyl glyoxylate have been identified in the reaction product. The formation of the last named compound may be accounted for by the following reaction:

$$2HCN + 4HOC_2H_5 + 3HCl \rightarrow (C_2H_5O)_2CH.COOC_2H_5 + C_2H_5Cl + 2NH_4Cl$$

The formation of formate and diethoxyacetamide may be explained by assuming that the reaction takes place via the following steps:

$$\begin{aligned} C_2H_5OH &\rightarrow (C_2H_5)_2O + H_2O \\ HCN + C_2H_5OH + H_2O + HCl &\rightarrow HCOOC_2H_5 + NH_4Cl \\ 2HCN &\rightarrow HC(:NH).CN \\ HC(:NH)CN + 2C_2H_5OH + H_2O + HCl &\rightarrow HC(OC_2H_5)_2.CO.NH_2 + NH_4Cl \end{aligned}$$

Compounds of similar composition are obtained through the interaction of other alcohols with hydrocyanic acid. Thus, with isobutyl alcohol, one of the reaction products is isobutyldiisobutyl glyoxylate[3] $[(CH_3)_2.CH.CH_2O]_2.CH.COOCH_2.CH(CH_3)_2$.

In anhydrous ether or other inert solvents, hydrocyanic acid reacts with an exact equivalent of alcohol in the presence of hydrochloric acid to form formochloramino ethyl ether hydrochloride[4]:

$$HCN + HO.C_2H_5 + 2HCl \rightarrow CH(Cl)(NH_2).OC_2H_5.HCl$$

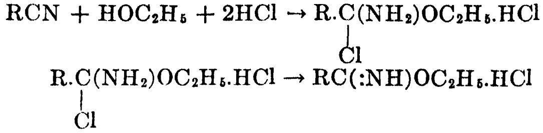
The compound is unstable and changes to formino ethyl ether hydrochloride:

$$CH(Cl)(NH_2).OC_2H_5.HCl \rightarrow CH(:NH).OC_2H_5.HCl + HCl$$

Care should be exercised in preparing the compound to avoid the presence of any excess alcohol, to cool efficiently during the introduction of gaseous hydrogen chloride, and to agitate the solution thoroughly in order to avoid any local overheating. It is important also to continue to cool the reaction product after the absorption of hydrochloric acid ceases, until conversion to iminoether hydrochloride is complete.

Formimino ethyl ether hydrochloride is a very unstable compound, and decomposes on exposure to the atmosphere even in the absence of moisture. It dissolves in alcohol, and is rapidly decomposed by the solvent.

Nitriles in general react with alcohols in the presence of hydrochloric acid to form iminoether hydrochlorides. The first product of the reaction is the hydrochloride of the chloroamine ester, which is unstable and rapidly decomposes to the iminoether hydrochloride:



$$RCN + HOC_2H_5 + 2HCl \rightarrow R.\underset{\substack{|\\ Cl}}{C}(NH_2)OC_2H_5.HCl$$

$$R.\underset{\substack{|\\ Cl}}{C}(NH_2)OC_2H_5.HCl \rightarrow RC(:NH)OC_2H_5.HCl$$

In preparing iminoethers, care should be exercised to use little more than the theoretically required quantities of alcohol and hydrogen chloride, and to dry thoroughly all materials used. If the nitrile is soluble in a molecular equivalent of the alcohol, hydrogen chloride is passed through a solution of equivalent amount of the nitrile in alcohol, otherwise a sufficient quantity of an auxiliary solvent not containing hydroxy groups, such as benzene or ether is used to dissolve the nitrile. The solution is then cooled and hydrogen chloride is passed through it. After the proper quantity of acid has been absorbed the liquid is allowed to stand for a few days, preferably first in a cold water-bath, then at ordinary temperature; it is then placed in a closed vessel over concentrated sulfuric acid and solid sodium hydroxide. If the iminochloride fails to crystallize out, the liquid is kept for a longer period in a shallow container over sulfuric acid and solid sodium hydroxide.

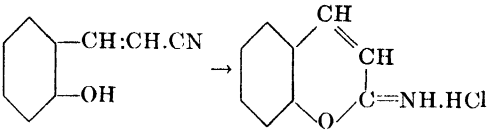
In preparing iminoethers from hydrogen cyanide and alcohols the solution must be diluted with ether as otherwise reaction proceeds with explosive violence. The solution should be cooled with ice or with ice-salt mixture. The alcoholic solution should also be cooled in this manner when preparing iminoethers from cyanogen.

All nitriles do not form iminoethers with equal ease. The same influences which cause variations in ease of hydrolysis would also appear to cause variations in the ease of formation of iminoethers. Pinner[5] observed that certain ortho-substituted benzonitriles failed to form iminoethers. Yamashita[6] confirmed this observation, and showed that the *m*- and *p*-substituted isomers yield iminoethers with phloroglucinol and resorcinol; that the presence of a substituent in ortho position, for example a nitro group in phenylacetonitrile, caused a retardation of the reaction velocity but did not prevent the formation of iminoether with phloroglucinol, although resorcinol failed to give an iminoether with the compound. Steinkopf and Malinowski[7] studied the effect of negative substituents on iminoether formation, and found that β- and γ-halogen-substituted nitriles behaved normally; trichloroacetonitrile, nitroacetonitrile, dichloroacetonitrile, tribromoacetonitrile and dichloronitroacetonitrile gave amides but no iminoethers. Dibromoacetonitrile gave both the amide and the imino-ether. Monohaloacetonitriles and dimethylnitroacetonitrile behaved normally.

Aminonitriles have been converted to iminoethers by treatment with alcoholic hydrochloric acid solution. Iminoethers have thus been prepared from glycine, benzoylglycine, $C_6H_5CO.NH.CH_2.CN$, chloracetyl glycine, $ClCH_2CONHCH_2$-CN, thiophenoylaminoacetonitrile, $C_4H_3S.NH.CH_2CN$, and *p*-toluenesulfonylaminoacetonitrile, $CH_3CH_4SO_2NH.CH_2CN$. The iminoether derived from glycine is unstable and polymerizes at ordinary temperature to a partially amorphous product[38].

Iminoether hydrochloride formation proceeds normally with primary and secondary alcohols and with phenols. Tertiary alcohols do not form iminoether hydrochlorides, but lose water to form unsaturated compounds.

Hydroxyl groups present in the δ-position, with respect to the cyano group interact with the latter to form imino-O-lactones. Thus, *o*-cumaric nitrile forms iminocumarin hydrochloride[8]



Benzoyl cyanide does not form an iminoether, but reacts with alcohols in the presence of hydrochloric acid to form a benzoic ester:

$$C_6H_5COCN + HOC_2H_5 \rightarrow C_6H_5COOC_2H_5 + HCN$$

Houben[9] prepared the hydrochlorides of the following iminoethers:

	Yield % *Theory*
Acetimino phenyl ether	55
Monochloroacetimino phenyl ether, $C_6H_5O(CH_2Cl):NH$	73
Dichloroacetimino phenyl ether, $C_6H_5O(CHCl_2):NH$	70
Trichloroacetimino phenyl ether, $C_6H_5O(CCl_3):NH$	74
Benzimino phenyl ether, $C_6H_5OC(:NH)C_6H_5$	60
Phenylacetimino phenyl ether, $C_6H_5O.C(:NH)CH_2C_6H_5$	42
Acetimino β-naphthyl ether, $C_{10}H_7O.C(:NH).CH_3$	45
Chloroacetimino β-naphthyl ether, $C_{10}H_7O\underset{\substack{\vert \\ CH_2Cl}}{C}{:}NH$	52

Pinner and Lohmann[10] have prepared the following iminoether hydrochlorides:

Propionimino isobutyl ether hydrochloride	$CH_3CH_2.C(:NH)OC_4H_9.HCl$
Acetimino ethyl ether hydrochloride	$CH_3.C(:NH).O.C_2H_5.HCl$
β-Naphthoimino ethyl ether hydrochloride	$C_{10}H_7.C(:NH).OC_2H_5.HCl$
β-Naphthoimino butyl ether hydrochloride	$C_{10}H_7.C(:NH)OC_4H_9.HCl$

Houben and Pfankuch[11] have prepared:

Formino methyl ether hydrochloride	$HC(:NH)OCH_3.HCl$, yield 90%
Formimino benzyl ether hydrochloride	$HC(:NH)OCH_2C_6H_5.HCl$, yield 89%
Formimino bornyl ether hydrochloride	$HC(:NH)OC_{10}H_{17}.HCl$, yield 80–85%
Acetimino borynl ether hydrochloride	$CH_3.C(:NH)OC_{10}H_{17}.HCl$
α-Hydroxyacetimino ethyl ether hydrochloride	$CH_2OH.C(:NH)OC_2H_5.HCl$, yield 89%
Lactimino ethyl ether hydrochloride	$CH_3.CH(OH).C(:NH)OC_2H_6HCl$
β-Chlorolactimino ethyl ether hydrochloride	$CH_2Cl.CH(OH):C(:NH)OC_2H_5.HCl$
Acetyl-β-chlorolactimino ethyl ether hydrochloride	$CH_2Cl.CH(OCOCH_3).C(:NH)OC_2H_5.HCl$
β-Chloro-α-ethoxylactimino ethyl ether hydrochloride	$CH_2Cl.CH(OC_2H_5).C(:NH)OC_2H_5.HCl$

Pinner[10] prepared succinimino ethyl ether hydrochloride from succinonitrile:

$$CN.CH_2.CH_2CN + 2HO.C_2H_5 + HCl \\ \rightarrow H_2N.C(OC_2H_5).CH_2CH_2.C(:NH)OC_2H_5.HCl$$

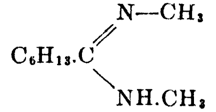
Pinner and collaborators[47] prepared in addition the iminoether hydrochlorides from the following nitriles: propionitrile, butyronitrile, isocapronitrile, stearonitrile, allylcyanide, lactonitrile, α-hydroxyisobutyronitrile, trichlorolactonitrile, $Cl_3CCH(OH)CN$, α-hydroxytrichlorovaleronitrile, $CH_3CHCl.CCl_2.CH(OH)CN$, glutaronitrile, furfuronitrile, tolunitrile, phenylacetonitrile, *o*- and *p*-methoxybenzonitriles, *o*- and *p*-ethoxybenzonitriles, naphthonitrile, iso- and terephthalonitriles, *p*-phenylenediacetonitrile, $C_6H_4(CH_2.CN)_2$, campholenic nitrile, $C_9H_{15}CN$.

Houben attempted to prepare the free phenol iminoethers without success.

Glock[12] prepared:

p-Tolenylimino ethyl ether hydrochloride.......	$CH_3.C_6H_4C(:NH)OC_2H_5.HCl$
Phenylene-*p*-diacetimino ethyl ether hydrochloride....................................	$C_6H_4[CH_2C(:NH)OC_2H_5.HCl]_2$
m-Cyano-*p*-tolenylimino ethyl ether hydrochloride....................................	$CH_3C_6H_3(CN).C(:NH)OC_2H_5.HCl$

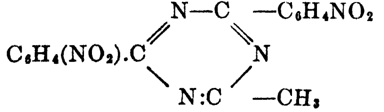
Pinner[13] prepared oenanthimino ethers from *oenanthonitrile*, $C_6H_{13}.CN$, with various alcohols. The salts crystallized with greater difficulty, the larger the molecule of alcohol. The amidine was obtained by the action of excess alcoholic ammonia upon the iminoether hydrochlorides. By the action of methylamine on heptenyl iminoether, *sym.*-dimethylheptenylamidine was obtained,



$$C_6H_{13}.C\begin{matrix}\nearrow\!\!\!\!\nearrow N{-}CH_3\\ \searrow NH.CH_3\end{matrix}$$

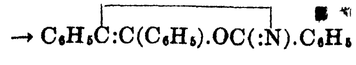
Oppenheimer[14] prepared iminoethers which were unusually unstable from *ethyl cyanoacetate*, but he failed to obtain iminoethers from *chloroacetonitriles*. Steinkopf[15] showed that *trichloroacetonitrile* forms the free methyl iminoether, $Cl_3C.C(:NH)OCH_3$, on heating a solution of trichloroacetonitrile in excess methanol to boiling for five hours. The ether is decomposed to the amide and $ClCH_3$ on treatment with hydrochloric acid.

Neubert prepared iminoethers from *nitrobenzonitrile;* Kunze obtained the corresponding amidines and various other derivatives from these compounds, in particular dinitrophenylmethylcyanidine,[16]



Beyer[17] prepared mandelimino ethyl ether, $C_6H_5CH(OH).C{:}NH.COOC_2H_5$, m.p. 71–72°; *m*-nitromandelimino-ethyl ether, m.p. 84°; and from these the corresponding amidines.

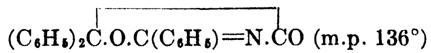
The iminoethers formed by the interaction of *benzoïn* and *nitriles* in the presence of acids condense to oxazoles. Thus, with benzonitrile, 4,5-diphenyl-2-phenyloxazole, m.p. 115°, is obtained:



$$C_6H_5CO.CH(OH)C_6H_5 + NCC_6H_5 \rightarrow C_6H_5.CO.CH(C_6H_5)O.C(:NH).C_6H_5$$
$$\rightarrow C_6H_5C{:}C(C_6H_5).OC(:N).C_6H_5$$

4,5-Diphenyloxazole, m.p. 44°, 4,5-diphenyl-2-methyloxazole, m.p. 28° and 4,5-diphenyl-2-ethyloxazole, m.p. 32°, have also been prepared by the condensation of benzoïn with hydrocyanic acid, acetonitrile and propionitrile, respectively[18].

2,5,5-Triphenyl-4-oxazolone,



$$(C_6H_5)_2C.O.C(C_6H_5){=}N.CO \text{ (m.p. } 136°)$$

results through the interaction of benzilic acid and benzonitrile in the presence of concentrated sulfuric acid[49].

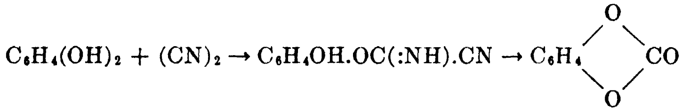
Cyanogen and ethyl alcohol react at 0° in the presence of potassium cyanide, forming principally cyanoformimino ethyl ether, $CN.C(:NH).OC_2H_5$. In the presence of sodium ethylate, the main product of the reaction is oxalimino ethyl ether[19], $C_2H_5OC(:NH).C(:NH)OC_2H_5$. *Allyl alcohol* combines directly with one molecule of cyanogen, forming a compound which is probably cyanoformimino allyl ether, $CN.C(:NH)OCH_2CH:CH_2$.

Picramic acid reacts with cyanogen in alcoholic solution, forming ethoxycarbimidamidodinitrophenol[20]:

$$NH_2C_6H_2(NO_2)_2OH + (CN)_2 + C_2H_5OH \rightarrow C_2H_5O.C(:NH).NH.C_6H_2(NO_2)_2OH + HCN$$

Aqueous solutions of *acetaldehyde* react with cyanogen, forming vinyloxamide, $H_2NCO.C(:NH)O.CH:CH_2$. This compound gives, on hydrolysis, oxamide and acetaldehyde.

Pyrocatechin, alone among the three dihydroxy benzenes, reacts with cyanogen to form a monocyano derivative which cannot be hydrolyzed to a carboxylic acid by the usual treatment. On hydrolysis with caustic soda pyrocatechin is regenerated and one molecule of sodium cyanide forms[21]. In aqueous solution the reaction between pyrocatechin and cyanogen probably proceeds as follows[22]:



$$C_6H_4(OH)_2 + (CN)_2 \rightarrow C_6H_4OH.OC(:NH).CN \rightarrow C_6H_4{<}\overset{O}{\underset{O}{\ }}{>}CO$$

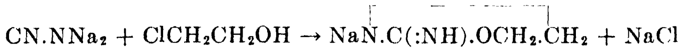
$$C_6H_4(OH).C(:NH).CN + C_6H_4(OH)_2 \rightarrow C_6H_4(OH).OC(:NH).C(:NH)O.C_6H_4OH$$

Phenol and its homologs do not react with cyanogen or they react to form highly unstable compounds[21]. α-Naphthol does not react with cyanogen, but β-naphthol forms a compound melting at 109–110°[22].

Cyanamide, reacting with *methyl alcohol* in the presence of hydrogen chloride, is converted quantitatively to methylisourea[40], $H_2NC(:NH)OCH_3$. *Iso*ureas result, in general, from the interaction of alcohols, functional derivatives of alcohols or phenols with a mixture in equimolecular proportions of cyanamide and cyanamide hydrochloride[56]. Reaction takes place also with polyhydric alcohols and with alcohols containing other functional groups[57]. *Pseudo*ureas are obtained in good yield when phenols are made to react with cyanamide dihydrochloride in anhydrous media. Thus 0-*m*-tolyl *pseudo*urea, m.p. 215–216° (dec.) is obtained in 80% yield by proceeding in the following manner:

Dry hydrogen chloride is passed through a mixture of 75 cc *m*-cresol and cyanamide dihydrochloride, $CNNH_2.2HCl$, for one hour at ordinary temperature. The mixture is then heated at 140° for four hours, the temperature being finally raised to 150–155°. The reaction product is filtered and extracted with cold, dilute acid. The unreacted cresol is removed by steam distillation, and the residual liquid is concentrated and cooled to crystallization[58].

Sodium cyanamide reacting with 1,2-chlorohydrins or alkylene oxides gives 2-iminooxazolidines:



$$CN.NNa_2 + ClCH_2CH_2OH \rightarrow NaN.C(:NH).OCH_2.CH_2 + NaCl$$

Alcoholic ammonia converts these compounds to β-hydroxyethyl guanidines[50].

Phenyl cyanamide reacst with ethyl alcohol in the presence of hydrochloric acid forming phenylethyl*iso*urea hydrochloride, $C_6H_5NHC(:NH)OC_2H_5.HCl$, in quantitative yield. The reaction is best carried out in dilute absolute alcoholic solution. Hydrolyzed with acids, the compound yields phenylurea[59].

Iminoethers may be prepared from *thiocyanates*. It is necessary, however, to observe the usual precautions: All moisture should be eliminated and the theoretical quantity of alcoholic hydrochloric acid should be used. Yields of iminoether range between 30 and 50%. The hydrochlorides of these iminoethers are colorless and odorless solids, which are converted by water to thiocarbamates. The free iminoethers are liquids that may be distilled under vacuum without decomposition. They are obtained by treating an ethereal solution of the hydrochloride with an aqueous solution of potassium carbonate. Knorr[41] prepared iminoethers, $R_1SC(:NH)OR_2$, in which R_1 and R_2 were respectively C_2H_5—, C_2H_5—; C_6H_5, C_2H_5—; C_6H_5, *iso*-C_4H_9—; CH_3—, CH_3—; C_2H_5—, CH_3—; C_4H_9—, C_2H_4— and CH_3—, C_2H_5—.

Reactions of Iminoethers. Iminoether hydrochlorides are decomposed by water to an amide and alcohol:

$$RC(:NH)OR'.HCl + H_2O \rightarrow RCONH_2 + R'OH + HCl$$

The lower aliphatic members are decomposed almost instantaneously, but the higher homologs and aromatic iminoethers are decomposed gradually, and in some cases decomposition takes place rapidly only upon boiling the aqueous solution of the compound.

The free iminoethers, $RC(:NH)OR'$, reacting with water give what were originally considered to be iminohydrins, $RC(NH)OH$, but were later demonstrated to be dimolecular compounds which in aqueous solution were good conductors of electricity. Rule established the true character of these compounds, showing that they were simply the amidine salts[51], $RC(:NH)NH_2.RCOOH$.

Iminoether hydrochlorides are decomposed by alcohols, decomposition taking place slowly in general, with the formation of an ester and ammonium chloride. Reaction takes place rapidly with formimino ethyl ether hydrochloride and ethyl alcohol, resulting in the formation of ethyl orthoformate.

Acetic anhydride reacts with iminoether hydrochlorides replacing the alkyl group with the acetyl group:

$$RC(:NH)OC_2H_5.HCl + O(COCH_3)_2 \rightarrow RC(:NH)OCOCH_3 + CH_3COOC_2H_5 + HCl$$

Iminoethers react with ammonia and amines in general, to form simple or substituted amidines:

$$HC(:NH)OC_2H_5 + NH_3 \rightarrow HC(:NH)NH_2 + HOC_2H_5$$
$$HC(:NH)OC_2H_5 + H_2NCH_3 \rightarrow HC(:NH)NHCH_3 + HOC_2H_5$$
$$CH_3.C(:NH)OC_2H_5 + H_2N.C_6H_5 \rightarrow CH_3.C(:NH)NHC_6H_5 + HOC_2H_5$$

A substituted amine may also replace the imino group in iminoether hydrochlorides forming a substituted iminoether:

$$RC(:NH)OC_2H_5.HCl + H_2NR' \rightarrow RC(:NR')OC_2H_5.HCl + NH_3$$

This on further reaction with the amine may form a disubstituted amidine hydrochloride, $RC(:NR')NHR'.HCl$. Forminoethers and ammonia give a quantitative yield of formamidine[23].

Pinner obtained succinamide on treating succiniminodiethyl ether hydrochloride with aqueous ammonia; he prepared *succinamidine* by treatment of succinimino diethyl ether hydrochloride with alcoholic ammonia:

$$C_2H_5OC(:NH)CH_2.CH_2C(:NH)OC_2H_5.2HCl + 2NH_3 \rightarrow H_2NC(:NH)CH_2.CH_2C(:NH)NH_2.2HCl + 2CH_3OH$$

It was necessary to keep the crystals of the compound in contact with alcoholic ammonia for eight days.

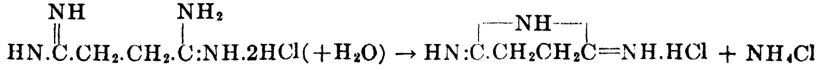
Lamb and White[24] prepared a number of *dicarboxamidines* from the corresponding dinitriles:

Decane-1,4-dicarboxamidine*	
Decane-bis-N,N'-diphenylcarboxamidine	m.p. 163–5°
N-Cyclohexyl analog†	m.p. 122°
Tetradecanocarboxamidine-HCl	m.p. 138°

Pyman and Levene[25] similarly prepared amidines corresponding to the general formula, $R_1R_2N(CH_2)_nC(:NH).NH_2$, in which R_1, R_2 were hydrogen, or alkyl groups, and *n* was an integer 7 to 13, from the corresponding nitriles, by conversion to the iminoether hydrochlorides followed by reaction with ammonia. The compounds prepared were the following:

κ-Dibutylaminoundecaneamidine
λ-Dibutylaminododecaneamidine
λ-Diethylaminododecaneamidine
κ-Butylaminoundecaneamidine
κ-Aminoundecaneamidine

On crystallizing succinamidine hydrochloride from water, Pinner obtained succinimidine hydrochloride[26]:



$$HN.\overset{\overset{NH}{\|}}{C}.CH_2.CH_2.\overset{\overset{NH_2}{|}}{C}:NH.2HCl(+H_2O) \rightarrow HN:\overset{\ulcorner\text{—NH—}\urcorner}{C.CH_2CH_2C}=NH.HCl + NH_4Cl$$

---

* The dihydrochloride melts at 87°.

† The dihydrochloride melts at 273°.

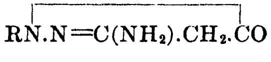
Pinner and Klein[1] prepared *benzamidine hydrochloride* from butyl benziminoether. The iminoether adds a molecule of hydrochloric acid to form a chloroaminoether:

$$C_6H_5C(:NH)OC_4H_9.HCl + HCl \rightarrow C_6H_5C(NH_2)(Cl).OC_4H_9.HCl$$

Diamidines, $H_2NC(NH)C_6H_2CR'{=}CR''C_6H_2C(NH)NH_2$, have been prepared similarly from the corresponding dinitriles[52].

Nicotinamidine has been prepared from the nitrile of nicotinic acid by conversion first to nicotiniminoether and subsequent reaction with ammonium chloride[39].

Ethyl iminoether derived from ethyl cyanoacetate, reacting with phenylhydrazines, $RNH.NH_2$, gives 1-substituted 3-aminopyrazolones[53],



$$RN.N{=}C(NH_2).CH_2.CO$$

Hydroxylamine and aromatic hydrazines may replace the alkyl or imino group in iminoethers forming compounds of the following type: $RC(:NOH)NH_2$, $RC(:NOH)OR'$, $RC(NH_2):N.NHR''$, $RC(OR'):N.NHR''$.

Simple chloroaminoethers are quite unstable; they become more stable when the hydrogen atoms in the amino group are replaced by alkyl groups, as in $RCCl(NEt_2)OC_2H_5.HCl$. The substituted chloroaminoethers are decomposed by heat giving first the iminoether hydrochloride, then finally the nitrile[27]:

$$R.CCl(NEt_2)OC_2H_5.HCl \rightarrow R.C(:NEt)OC_2H_5.HCl + EtCl$$
$$R.C(:NEt)OC_2H_5.HCl \rightarrow RCN + Et.Cl + EtOH$$

Iminoether hydrochlorides may be hydrolyzed to the corresponding esters. Thus, according to British patent 325,531 (1930—I.G.), ethyl lactate may be obtained from lactimino ethyl ether by the hydrolysis in benzene solution with the required quantity of water:

$$CH_3.CH(OH)C(:NH)OC_2H_5.HCl + H_2O \rightarrow CH_3CH(OH)CO.OC_2H_5 + NH_4Cl$$

Aldehydes are formed when iminoethers are reduced with sodium amalgam in acid solution[45]. Reduced electrolytically in 2*N* sulfuric acid solution, iminoethers give amines: the following amines have been prepared by this method from the corresponding nitriles in the yields indicated[46]:

	Yield, %
Benzylamine	76
m-Tolubenzylamine	70
p-Tolubenzylamine	94
Ethylamine	16
Phenylethylamine	14
p-Ethoxybenzylamine	66

Direct Formation of Esters from Nitriles

Esters may be obtained from nitriles directly by the simultaneous action of an alcohol and water in the presence of a mineral acid:

$$R_1CN + H_2O + HOR_2 + HCl \rightarrow R_1COOR_2 + NH_4Cl$$

Beckurtz and Otto[28] were among the earliest investigators to prepare esters by this method. Spiegel[29] carried out a systematic study of the reaction, and concluded that the best proportions of nitrile, alcohol and acid (sulfuric) are 1:2:1. In some instances better results are obtained, however, by using a larger proportion of alcohol, sometimes as much as 10 moles of alcohol to 1 mole of nitrile. Spiegel obtained butyric ester in 90% yield by heating the mixture of alcohol, butyronitrile and sulfuric acid for three hours. Good yields of ester were also obtained by heating one molecular equivalent of nitrile, one of acid and ten of alcohol in a sealed tube at 130–140°. Certain esters are prepared on a large scale by this method.

U. S. patent 1,650,950 (1927) and French patent 620,807 (1927) to the Canadian Electro Products Company cover the process of manufacturing lactic esters from aldehyde cyanohydrin, alcohol and water in the presence of a mineral acid. A similar process is covered by U. S. patent 1,790,262 (1931) British patent 325,531 (1930) to I. G. Farbenindustrie, A. G.; French patent 699,675 (1931) to Aktiengesellschaft für Stickstoffdünger; and German patents 544,499; 562,390 (1932) to I. G. Farbenind., A. G.

Pfeiffer[30] prepared esters from various nitriles derived from stilbene and isatogen with alcoholic hydrochloric acid, and observed that substituents in the ortho position with respect to the CN-group, prevented the formation of ester.

Pfeiffer[31] prepared the methyl ester of *o*-nitrostilbene *p*-carboxylic acid by allowing a solution of *p*-cyano-*o*-nitrostilbene in methyl alcohol saturated with hydrogen chloride to stand for a number of hours, then pouring the liquid in water, whereby the ester separated out.

Spiegel[29] in preparing esters from various aromatic nitriles and alcoholic sulfuric acid, similarly noted that the presence of a methyl group in the ortho position with respect to the CN-group retarded the reaction. Steric hindrance is thus observed here as in the hydrolysis of nitriles or the formation of iminoethers.

It is probable that ester formation from nitriles is preceded by the formation of an iminoether, which subsequently is hydrolyzed with the water present to an ester, with the formation of the ammonium salt of the inorganic acid employed. Side-reactions may occur to complicate the course of the reaction. Thus, the alcohol may react with the acid to form an inorganic ester which, if volatile, escapes causing a material loss of alcohol and acid. This will be the case, for example, when preparing a methyl ester by the use of hydrochloric acid and methanol. Certain alcohols, *e.g.*, the secondary alcohols, tend to form unsaturated hydrocarbons with the loss of a molecule of water under the conditions of reaction and thus may fail to yield an ester. Hydroxynitriles show a tendency to form estolides, or inner esters.

Aromatic nitriles with substituents in the ortho position are not esterified with methyl alcohol and hydrogen chloride, or are esterified with difficulty. Thus, benzonitrile and para- and meta-tolunitriles are readily esterified, but ortho-tolunitrile cannot be converted to the ester. The same holds true of the ortho-nitro- and ortho-chlorobenzonitriles. α-Naphthonitrile cannot be esterified, whereas β-naphthonitrile is readily converted to the ester[32].

The *trans*-isomer of phenylcinnamonitrile and nitrophenylcinnamonitrile are readily esterified, whereas the *cis*-isomers of these compounds cannot be esterified[33].

Reaction of Nitriles with Mercaptans and Other Thio-Compounds. In the presence of mineral acids, mercaptans react with nitriles in the same way as alcohols, to form iminothioethers[48]:

$$R_1CN + HSR_2 + HCl \rightarrow R_1C(:NH).SR_2.HCl$$

Thiophenols react in a similar manner. Autenrieth and Brüning[34] have prepared thioformimino phenyl ether from hydrocyanic acid and thiophenol:

$$HCN + HS.C_6H_5 + HCl \rightarrow C_6H_5S.CH:NH.HCl$$

These authors also prepared phenylthioethers with acetonitrile, propionitrile, succinonitrile, benzonitrile and phenyl acetonitrile.

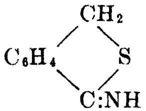
Iminothioethers have been prepared from benzonitrile and methyl, propyl, isoproply, butyl, isobutyl, *tert*-butyl and amyl mercaptans[1]. The yields are good except with *tert*-butyl mercaptan. Upon heating, they decompose to thiobenzamide and an alkyl halide, though less readily than the corresponding oxy ethers. They react normally with water forming thiol esters[54].

Thioacetic acid reacts with benzonitrile to form thiobenzamide and benzimidoisothiobenzamide[35].

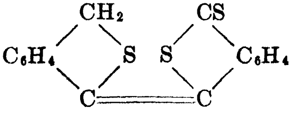
Houben and Zivadinovitsch[36] prepared the following iminothioethers:

	M.P. °*C*	*Yield* *% of Theory*
Formimino benzyl thioether hydrochloride, $HC(:NH)SCH_2.C_6H_5.HCl$	dec. 180	70
Formhydroximino ethyl thioether, $HC(:NOH).SC_2H_5$	110–111	31
Formhydroximino *n*-butyl thioether	90–91	20
Formhydroximino benzyl thioether	116–117	
Acetimino benzyl thioether hydrochloride, $CH_3C(:NH)SCH_2C_6H_5.HCl$	153–155	theoretical
Acetiminothioglycolic ethyl ether hydrochloride, $CH_3C(:NH)SCH_2CO_2C_2H_5.HCl$	100–102	good
Acetiminothioglycolic acid hydrochloride, $CH_3C(:NH)SCOOH.HCl$	110–112	fair

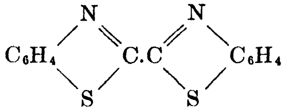
o-Cyanobenzyl chloride, reacting with potassium acid sulfide, forms *o*-cyanobenzylmercaptan which changes to



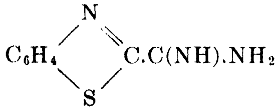
and finally to a compound of the empirical formula, $C_{16}H_{10}S_3$, which is probably[42]



Cyanogen reacts with *ortho*-aminophenylmercaptan in excess, forming the compound



The compound



forms when a deficiency of the mercaptan is used[37].

Mercaptans react with cyanamide to form isothioureas:

$$H_2NCN + HSR \rightarrow H_2NC(:NH)SR$$

p-Tolyl-, benzyl- and phenylisothioureas have been made by this method[43].

Reaction with Aldehydes. Nitriles react with aldehydes in aqueous solution in the presence of strong mineral acids forming compounds of the probable composition $[R_1C(:NH)O]_2CHR_2$:

$$2CH_3CN + CH_3CHO + H_2O + 2HCl \rightarrow [CH_3C(:NH)O]_2CH.CH_3.2HCl$$

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Chapter 6

Reaction of Nitriles with Halogens and Other Negative Elements: Reactions of Cyanogen Halides and Cyanamides

REACTION OF NITRILES WITH HALOGENS AND OTHER NEGATIVE ELEMENTS

Reaction of Hydrocyanic Acid with Halogens

Halogens can replace the hydrogen in hydrocyanic acid to form cyanogen halides. Thus, reacting with hydrocyanic acid in dilute aqueous solution, chlorine forms cyanogen chloride:

$$HCN + Cl_2 \rightarrow Cl.CN + HCl$$

Gautier[1] prepared the compound by the action of chlorine on a solution of one volume of hydrocyanic acid in five volumes of water. When higher concentrations of hydrocyanic acid were treated with chlorine, the yield of cyanogen chloride decreased, due to side reactions. Gautier also obtained cyanuric chloride by treating an ethereal solution of cyanogen chloride with hydrogen chloride.

The reaction proceeds largely to completion with chlorine[2] and bromine, while with iodine the reaction proceeds only partially. Cyanogen iodide dissociates to an appreciable extent into iodine and hydrocyanic acid[3]. Cyanogen halides also form readily by the interaction of alkali cyanides in aqueous solution with chlorine[4]:

$$NaCN + Cl_2 \rightarrow ClCN + NaCl$$

Formation of dark polymerization products is avoided by gradually adding alkali cyanide in aqueous solution to water through which is passed a current of chlorine under external cooling. The cyanide is added at such a rate that there is an excess of chlorine present in the reaction mixture at all times.

Sodium cyanoforminino chloride, $CN.C(Cl){:}NHa$, m.p. 95°, is obtained when a current of chlorine is passed into an aqueous solution of sodium cyanide until the solution assumes an orange-red color[105]. The reaction of cyanogen chloride with sodium cyanide is reported to yield paracyanogen[106].

In alcoholic solution, hydrocyanic acid reacts with chlorine to form the compounds[5], $CH_2Cl.CH(NHCO_2.C_2H_5)_2$, and $CHCl_2.CH(NH.CO_2.C_2H_5)_2$. A similar reaction takes place with bromine, but not with iodine.

Aqueous alcoholic solutions of cyanogen chloride and cyanogen bromide react gradually with silver nitrate to form silver halide.

Bromine reacts with an ice-cooled solution of HCN in benzene with evolution of HBr to form a pasty, orange-red solid, and a small quantity of BrCN which remains in solution in benzene. The nature of the solid has not been established[6].

The iminoether of cyanoformic acid forms when a current of chlorine is conducted through an aqueous alcoholic solution of potassium cyanide, cooled to −5 to −10°:

$$2KCN + Cl_2 \rightarrow KN{:}CCl.CN$$
$$KN{:}CCl.CN + C_2H_5OH \rightarrow HN{:}C(CN).OC_2H_5 + KCl$$

Further alcoholysis takes place upon the addition of potassium cyanide to the solution of the iminoether, with the formation of diethyl diiminooxalate:

$$HN{:}C(CN)OC_2H_5 + HOC_2H_5 \rightarrow C_2H_5O.C({:}NH).C({:}NH)OC_2H_5$$

This compound is hydrolyzed with dilute hydrochloric acid to diethyl oxalate. With alcoholic sodium ethoxide solution, oxaldiiminoethyl ether gives diethyl iminocarbonate:

$$C_2H_5O.C({:}NH).C({:}NH).OC_2H_5 + NaOC_2H_5 \rightarrow (C_2H_5O)_2C{:}NH + NaCN + C_2H_5OH$$

Preparation of Cyanogen Chloride. Price and Green[7] prepared cyanogen chloride by the action of chlorine on a 12 to 15% solution of hydrocyanic acid in water. The reaction vessel was not cooled, the heat of reaction being utilized to distill off the cyanogen chloride formed; in this manner, hydrolytic decomposition, or polymerization due to the action of hydrochloric acid, was avoided. Reaction takes place almost instantaneously and the chlorine is rapidly absorbed. The current of chlorine is so adjusted that no gas escapes from the reaction vessel. The transformation of hydrocyanic acid to cyanogen chloride is quantitative.

Price and Green also prepared cyanogen chloride by adding a solution of sodium cyanide to one containing a small amount of sulfuric acid and chlorinating the hydrocyanic acid formed. The current of chlorine and the rate of addition of sodium cyanide solution were so adjusted that the solution was decidedly acid at all times. This method, though feasible, presented certain difficulties; thus, the heat effect was great and effective cooling was a problem, particularly when large quantities were to be dealt with. Also, the proper regulation of the current of chlorine and the rate of addition of the sodium cyanide solution was difficult.

Cyanogen chloride melts at −6.5° and boils at 12.6°. The molecular heat of vaporization at the boiling temperature is 6358 Cal.; the density of the liquid is 1.222 at 0° and 1.1963 at 12.6°. The liquid is only slightly soluble in water but it is miscible with alcohol and other organic solvents.

Cyanogen chloride has a strong lachrymatory effect, which makes it impossible for one to remain long in space containing high concentrations of the vapors of the compound. Cyanogen halides do not seem to possess the strong anaesthetic power of hydrocyanic acid, which causes rapid loss of consciousness in persons inhaling high concentrations of the latter. Chronic symptoms produced by cyanogen chloride are more severe than in the case of hydrocyanic acid, and death may follow chronic poisoning by the former. The lethal effect is attributed to the cyano group, and antidotes for cyanide poisoning are considered to be effective when poisoning is caused by cyanogen halides[107].

Cyanogen chloride is stable in the pure form, but polymerizes to cyanuric chloride in the presence of hydrogen chloride. The rate of polymerization increases with increase in the concentration of the acid and with rise in temperature. The transformation is accompanied with the evolution of considerable heat, and for this reason polymerization may proceed with explosive violence if liquid containing a comparatively large proportion of the acid is kept in a closed container.

Preparation of Other Cyanogen Halides[8]. Cyanogen bromide or iodide may be prepared by passing a current of gaseous chlorine through an aqueous solution containing an alkali cyanide and a metallic bromide or iodide. Since cyanogen halides are converted by alkali cyanides into paracyanogen and azulmic products, the cyanide should be introduced into the solution at the rate at which the halogen is generated.

Cyanogen bromide may be prepared conveniently by adding dropwise a solution of 65 grams of potassium cyanide in 120 grams water to 130 grams of bromine covered with a little water and cooled in ice. Any excess bromine is destroyed by the careful addition of more potassium cyanide solution until the bromine color just disappears. The cyanogen bromide formed is recovered by distillation in the form of white needles. It may be obtained in an anhydrous condition by a second distillation over calcium chloride.

Pure cyanogen bromide is stable. The compound gradually polymerizes in the presence of halogen acids. Polymerization may take place with explosive violence in the presence of comparatively large quantities of the acids.

Cyanogen bromide melts at 51.3° and boils at 61.3°. The density of the liquid at the boiling temperature is 1.8633; the coefficient of expansion is 1.452×10^{-3} per degree.

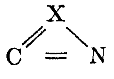
Grignard and Crouzier[8] prepared *cyanogen iodide* as follows: one half of a solution of 25 gm of sodium cyanide in 500 cc of water was added drop by drop and under agitation into a suspension of 63 gm of iodine in 100 cc of water. The remainder of the cyanide solution was then added, and a current of chlorine was passed through the reaction mixture at such a rate that some free iodine was present in the liquid throughout the entire reaction period. The passage of chlorine was continued until the reaction was complete. This was indicated by the fact that chlorine was no longer absorbed. The yield was 88.9% of theoretical.

Cyanogen fluoride has been obtained in 25% yield through the interaction of cyanogen iodide and silver fluoride in a sealed tube at 220°. It is a solid with a penetrating odor. Its vapors attack the mucous membrane of the eyes causing tears. It may be stored in glass containers and does not attack mercury. It sublimes at 72°[108].

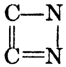
Possible Isomeric Forms of Cyanogen Halides. Two isomeric forms of cyanogen chloride were thought to exist at one time. Mauguin and Simon[9] prepared cyanogen chloride by six different methods, and arrived at the conclusion that only one molecular variety exists. Zappi advanced the view that cyanogen chloride has the isonitrile structure, that cyanogen iodide has the normal nitrile structure[10], and that cyanogen bromide occupies an intermediate position and exists in both forms[11],

$$\mathrm{BrC{\equiv}N \leftrightarrows Br.N{=}C}$$

Gutman[12] assigned to cyanogen halides the structure



where X is a halogen atom. Dixon and Taylor[13] assigned a similar structure to cyanogen,



Reaction of Hydrocyanic Acid with Sulfur

Hydrocyanic acid does not react with sulfur in the temperature range 25–160°. Reaction takes place readily in the presence of pyridine or other bases resulting in the formation of the thiocyanate of the base. Selenium reacts under the same conditions to form selenocyanates[14].

The reaction of sulfur with alkaline or alkaline earth cyanides proceeds at an appreciable rate only at elevated temperatures[15]:

$$KCN + S \rightarrow KSCN$$
$$Ca(CN)_2 + 2S \rightarrow Ca(SCN)_2$$

The reaction may be carried out either by heating the aqueous solution of cyanide with ground sulfur, or by fusing an intimate mixture of solid cyanide with ground sulfur.

Hydrocyanic acid reacts with certain disulfides, such as cystine and glutathione to form thiols. This reaction would appear to be a case of hydrocyanolysis and not one of reduction. Alkaline cyanides react similarly and more rapidly[16].

Reaction of Hydrocyanic Acid with Oxidizing Agents

Direct oxidation of hydrocyanic acid to cyanic acid may be accomplished with hypobromous acid. The reaction is complicated by the simultaneous formation of formic acid and carbon dioxide[17].

Attfield[18] and Radziszewski[19] state that the oxidation of hydrocyanic acid with hydrogen peroxide leads to the formation of oxamide, $(OCNH_2)_2$. Rupp and Pfenning[20] claim, on the other hand, that the products of the reaction are carbon dioxide and ammonia.

In the presence of a trace of potassium cyanide, cyanogen is converted quantitatively to oxamide by hydrogen peroxide[19].

Alkali cyanides may be oxidized by aqueous alkaline or acid permanganate solution yielding a number of products[21]. Volhard[22] showed that the main product of the reaction is alkali cyanate (about 68% of theory). Copper hydroxide acts as a catalyst, and good yields of cyanate may be obtained[23].

Alkali cyanides may be oxidized at a high temperature to alkali cyanates. Cyanates were, in fact, first obtained by Vauquelin in 1818 by this method. The reaction is favored by certain metallic oxides, for example those of lead or manganese.

Cyanates may also be obtained by the reaction of cyanogen chloride with an alkali:

$$Cl.CN + 2NaOH \rightarrow NaOCN + NaCl + H_2O$$

Alkali thiocyanates are obtained similarly by the reaction of alkali sulfides with cyanogen chloride.

Potassium cyanide in aqueous solution is oxidized by hydrogen peroxide largely to potassium cyanate and carbonate, some potassium formate being also formed[24]. The reaction is exothermic and may proceed violently unless external cooling is applied.

Cyanogen bromide reacts with alkalies to form a cyanide, bromide and bromate of the alkali metal:

$$3CNBr + 6NaOH \rightarrow 3NaCN + 2NaBr + NaBrO_3 + 3H_2O$$

With alkali metal sulfides, however, cyanogen bromide reacts in a manner similar to cyanogen chloride, forming sodium thiocyanate and sodium bromide[25]:

$$CNBr + Na_2S \rightarrow NaSCN + NaBr$$

Cyanogen bromide reacts with hydrogen sulfide to form hydrocyanic acid, hydrobromic acid and elemental sulfur[26].

Cyanogen iodide reacts with alkali hydroxides to form a cyanide, iodide and iodate[26].

Catalytic Oxidation of Hydrocyanic Acid. Sinozaki and Hara[27] studied the oxidation of hydrocyanic acid in the presence of a large number of catalysts, among others platinum, porcelain, and various metallic oxides. These authors also studied the catalytic action of mixtures of certain of these substances. With all of these materials, excepting porcelain, oxidation proceeded too vigorously and the products of reaction were carbon dioxide, carbon monoxide and nitric oxide. With the less active catalysts, cyamelide, $(CNOH)_n$, and cyanuric acid, $(CNOH)_3$, were obtained.

Electrolytic Oxidation of Aromatic Nitriles. Fichter and Grisard[141] studied the electrolytic oxidation of certain aromatic nitriles at a lead oxide anode. Benzonitrile was partially degraded and partially converted into cyanides of hydroquinone and pyrocatechin; *o*-, *m*- and *p*-tolunitriles yielded *o*-, *m*- and *p*-cyanobenzoic acid in 6, 28 and 14.5% yield respectively together with dark resinous products.

Reaction of Nitriles with Halogens

Engler[28] obtained monobromoacetimidobromide, $C_2H_3NBr_2$, by the action of bromine on acetonitrile; he also prepared the corresponding amidobromide from propionitrile. Ghigi[29] attempted to brominate acetonitrile by adding bromine slowly to a mixture of the nitrile red phosphorus and calcium carbonate. He obtained 2,4,6-tris-(dibromomethyl)-1,3,5-triazine,

$$Br_2CH.\overline{C{:}N.C(CHBr_2){:}N.C(CHBr_2){:}N} \text{ (m.p. 127–128°)},$$

in a low yield and a very small amount of dibromacetamide, α-Brominated nitriles are obtained in a yields ranging from 85 to 95% from aliphatic nitriles with four to thirteen carbon atoms. Other brominated nitriles are formed simultaneously, and the α-compounds obtained by this method have not been isolated in a pure form[97].

Backunts[30] was unable to chlorinate acetonitrile at ordinary or at boiling temperature. Acetonitrile vapors may, however, be chlorinated in the temperature range 200 to 400° and in the presence of a chlorinating catalyst such as active carbon or active carbon impregnated with a halide of zinc, copper or an alkaline earth metal. With a mixture consisting of 3 to 4 moles of chlorine and 1 mole of acetonitrile, and at a space velocity of 0.5 to 5 volumes of vapor per volume of catalyst per minute, trichloroacetonitrile is the major product of the reaction, but a large proportion of the trimer and tetramer of this compound is also formed[109].

Chlorine reacts with propionitrile to form chloropropionitrile[31], $C_2H_4Cl.CN$. A certain amount of α,α-dichloropropionamide and the trimer of α,α-dichloropropionitrile are formed simultaneously. If the chlorination is carried out at the boiling point of the nitrile, less of the trimer is formed[31].

α-Chloroisobutyronitrile is obtained upon conducting chlorine into isobutyronitrile in direct sunlight at 45 to 65°[110]. Monochloronitriles are the main product of reaction when vapors of saturated aliphatic nitriles mixed with chlorine are passed through a reaction zone heated at 250 to 550°[111].

Iodoacetonitrile reacts with tertiary amines to form quaternary ammonium compounds. With dimethyl aniline the reaction proceeds as follows:

$$C_6H_5N(CN_3)_2 + ICH_2CN \rightarrow C_6H_5N(CH_3)_2(CH_2CN)I$$

$$C_6H_5N(CH_3)_2(CH_2CH)I + C_6H_5N(CH_3)_2 \rightarrow C_6H_5N(CH_3)CH_2CN + C_6H_5N(CH_3)_3I$$

Ortho-substituted amines do not give this reaction. Bromoacetonitrile reacting with pyridine in benzene solution gives cyanomethyl pyridinium bromide. A similar reaction also takes place with bromophenylacetonitrile and ethyl bromocyanoacetate[142]. Bromobenzoylacetonitrile, $C_6H_5COCHBrCN$, reacting with pyridine in the presence of benzoic acid gives cyanophenacylpyridimum benzoate, $C_5H_5N(OCOC_6H_5)$.-$CH(CN)COC_6H_5$, with the liberation of hydrogen bromide.

Chlorine reacts slowly with benzonitrile in direct sunlight, giving a mixture of chlorinated compounds; among these are α- and β-benzonitrile hexachlorides, $C_6H_5CN.Cl_6$, hexachlorochlorbenzonitrile, $ClC_6H_4CN.Cl_6$, and 1,2,4,5-tetrachlorobenzene. Appreciable reaction takes place only after several days[98].

REACTIONS OF CYANOGEN HALIDES

Among the characteristic reactions of cyanogen halides are those with primary and secondary amines, a hydrogen atom attached to the nitrogen being replaced by a CN-group according to the equation:

$$2R.NH_2 + ClCN \rightarrow RNH.CN + RNH_2.HCl$$

This reaction is quite general, though all amines do not react with equal ease Primary and secondary aliphatic amines react readily; primary aromatic amines, in which the aromatic group does not contain strongly negative substituents such as halogens or nitro groups, also react readily. Negative substituents in the aromatic ring diminish the reactivity of an aromatic amine in proportion to their number and also their degree of negativity.

Cyanogen halides react with alkali salts of a class of weakly acidic compounds, such as sulfides, mercaptides, phenolates, etc., replacing the alkali metal with a CN-group.

Although cyanogen halides may be considered analogs of halogens, they are incapable of causing direct substitution of hydrogen in aromatic or other hydrocarbons with a halogen or a cyano group. The cyano group can, however, be introduced in aromatic compounds by the simultaneous action of a cyanogen halide and aluminum chloride.

Reaction of Cyanogen Halides with Amines

Cyanogen halides react vigorously with ammonia and primary amines forming, at first, cyanamide and substituted cyanamides.

$$2NH_3 + XCN \rightarrow H_2N.CN + NH_3.HX$$
$$2RNH_2 + XCN \rightarrow RNH.CN + RNH_2.HX$$

There is no direct relationship between the velocity of the reaction and the strength of the nitrogen base. The velocity of reaction with cyanogen chloride increases in the series NH_3, CH_3NH_2, $(CH_3)_2NH$, $(CH_3)_3N$. The rate of reaction increases in the same direction in the corresponding ethylamine series, with the exception that diethylamine reacts somewhat more rapidly than triethylamine[112].

Cyanamide, the reaction product of ammonia and cyanogen chloride is itself unstable in alkaline solution, and may undergo polymerization to a dimer, dicyanodiamide, the rapidity of the transformation depending upon the conditions. Monosubstituted cyanamides are also unstable, and gradually polymerize on standing. The disubstituted cyanamides are comparatively stable.

Cyanamide and substituted cyanamides react with amine hydrochlorides with varying degrees of ease, forming guanidines.

Substituted thioureas have been prepared through the interaction of substituted cyanamides and hydrogen sulfide[32]:

$$R_1R_2N.CN + H_2S \rightarrow R_1R_2N.CS.NH_2$$

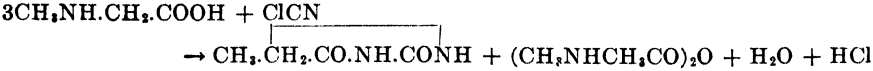
Cyanamide and methyl-, ethyl- and amylcyanamides have been obtained through the interaction of ammonia, methyl-, ethyl- and amylamines with cyanogen chloride[35].

Methylamine and cyanogen chloride react in ether solution forming symmetrical dimethylguanidine[33a], $(CH_3NH)_2C{:}NH$, which, in contrast with guanidine and other substituted guanidine, is a diacid base.

Secondary amines also react with cyanogen halides forming disubstituted cyanamides. Thus, dimethyl-, diethyl-, dipropyl- and diamylcyanamides have been prepared from the corresponding secondary amines and cyanogen bromide[32].

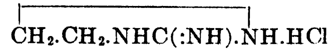
β-Chloroallylmethyl-, β-bromoallylmethyl- and *p*-bromobenzylmethylcyanamides have been prepared by treatment of the corresponding amines with cyanogen bromide[34].

Cyanogen chloride reacts slowly with *alanine* in aqueous solution, forming lacturic acid[35], $H_2NCONH.CH(CH_3)COOH$. Gaseous cyanogen chloride reacts with molten *sarcosine* forming a solid which consists of methylhydantoin and sarcosine anhydride[35]:



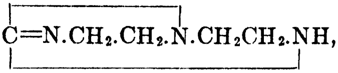
$$3CH_3NH.CH_2.COOH + ClCN \rightarrow CH_3.CH_2.CO.NH.CONH + (CH_3NHCH_2CO)_2O + H_2O + HCl$$

Ethylenediamine in aqueous solution, reacting at room temperature with an equimolecular quantity of cyanogen bromide, gives ethylene guanidine hydrochloride,



$$CH_2.CH_2.NHC(:NH).NH.HCl$$

Diethylene guanidine,



$$C{=}N.CH_2.CH_2.N.CH_2CH_2.NH,$$

results from the reaction of two molecules of ethylenediamine with one of cyanogen bromide[113].

Hydroxylamine in alcoholic solution reacts vigorously with cyanogen bromide at ordinary temperature. The products of reaction are hydrocyanic acid, nitrogen, carbon dioxide, ammonium bromide and hydrobromic acid:

$$2H_2NOH + 2BrCN \rightarrow HCN + N_2 + NH_4Br + HBr + CO_2$$

When the reaction is carried out at −20°, hydroxycyanamide is the principal product:

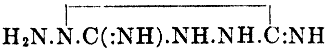
$$H_2NOH + BrCN \rightarrow CN.NH.OH + HBr$$

Hydroxycyanamide combines with unreacted hydroxylamine, forming dihydroxyguanidine[36]:

$$HONH.CN + H_2NOH.HBr \rightarrow (HONH)_2CNH.HBr$$

Phenylhydroxycyanamide, $C_6H_5.N(OH).CN$, has been prepared from a cold (0°) alcoholic solution of *phenylhydroxylamine* and cyanogen bromide; diphenyldihydroxyguanidine, $[C_6H_5.N(OH)]_2CNH$, m.p. 135°, has been prepared from this compound[37].

Cyanogen bromide and *hydrazine* reacting in molecular proportions form aminoguanazol,



$$H_2N.N.C(:NH).NH.NH.C:NH$$ [m.p. 257° (dec.)]

When the compounds are used in the ratio of one mole of cyanogen bromide and two moles of hydrazine, diaminoguanidine is the main product of the reaction, but some aminoguanazol also forms[99]. Diaminoguanidine may be obtained in good yield by treating a strongly cooled mixture of hydrazine and ether with the required quantity of gaseous cyanogen chloride and allowing the whole to stand for twelve hours. The compound separates as the hydrochloride, m.p. 174°, in the form of a voluminous white powder. The compound is obtained in a low yield if the reaction is carried out in aqueous solution. A white precipitate of $(NH_2NHCN)_3$ forms when an acetonitrile solution of cyanogen chloride is added to an alcoholic solution of hydrazine hydrate[100].

β-Cyanophenylhydrazine, $C_6H_5NH.NHCN$, forms through the interaction of cyanogen chloride and *phenylhydrazine* in cold ethereal solution. It is an unstable compound which polymerizes readily[38]. Phenylhydrazine, reacting in aqueous solution with cyanogen bromide, forms α-cyanophenylhydrazine, $C_6H_5N(CN).NH_2$, m.p. 89°, as well as phenylsemicarbazide, $C_6H_5NH.NHCONH_2$, and diphenyldiaminoguanidine hydrobromide[101], $(C_6H_5NH.NH)_2C{:}NH.HBr$. Reacting in alcoholic solution with cyanogen bromide at 60–70°, α-cyanophenylhydrazine gives phenyltricyanohydrazide, $C_6H_5.N(CN).N(CN)_2$, yellowish crystals melting above 300°.

Cyanogen halides react in the cold with aniline and other aromatic amines to form aromatic cyanamides[39]:

$$2C_6H_5NH_2 + Cl.CN \rightarrow C_6H_5NH.CH + C_6H_5NH_2.HCl$$

On prolonged heating of the mixture of the cyanamide and aniline hydrochloride at 100°, preferably in an inert solvent, diphenylguanidine results in excellent yield.

By passing cyanogen chloride into aniline heated nearly to boiling, a dark resinous product is obtained from which tetraphenyl melamine, m.p. 217°, may be extracted with boiling alcohol[114]. Pierron[40] prepared the following aromatic cyanamides by treatment of the corresponding amines with a molecular equivalent of cyanogen bromide in the presence of an aqueous solution of sodium bicarbonate:

m-Tolylcyanamide $(CH_3.C_6H_4.NH.CN)_2.H_2O$, m.p. 27°
o-Bromophenylcyanamide, m.p. 94°
m-Bromophenylcyanamide, m.p. 84°
p-Bromophenylcyanamide, m.p. 112°
m-Ethoxyphenylcyanamide[41], m.p. 57°
α- and β-Naphthylcyanamides, *m*-xylylcyanamide, *o*-, *m*-, and *p*-ethoxyphenylcyanamides[41]

m-Cyanamidobenzoic acid and *p*-cyanamidophenylacetic acid have been prepared by the action of cyanogen chloride on *m-aminobenzoic acid* and *p-aminophenylacetic acid*, respectively[35].

Ethyl anthranilate in ethereal solution, treated with cyanogen bromide, forms 2-cyanamidobenzoic ethyl ester[42], $CN.NH_2.C_6H_4COOC_2H_5$, m.p. 93–94°.

Nitrophenylcyanamides[43] have been prepared by heating an alcoholic solution of the *nitrophenylamines* with cyanogen bromide.

The *ortho-*, *meta-* and *para-*nitrocyanamides melt respectively at 146°, 130° and 180°. The following aromatic cyanamides have also been prepared:

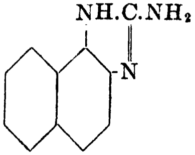
Methylphenylcyanamide, m.p. 28°[32]
Ethylphenylcyanamide[44]
Phenylpropylcyanamide[45], b.p.$_{12}$ 156–158°
*Iso*butylphenylcyanamide, b.p.$_{11}$ 130°[46]
Tetramethylenylphenylcyanamide, b.p.$_{12}$ 158°
*Pseudo*cumidylcyanamide[47], m.p. 126°
p-Hydroxyphenylcyanamide
p-Bromophenylethylcyanamide[48], m.p. 78°
Benzylcyanamide, m.p. 43°
Dibenzylcyanamide, m.p. 54°[32]

Piperidinocyanamide, b.p. 102°, has been prepared from *piperidine* and cyanogen bromide[32].

Diphenylamine in benzene solution does not react with cyanogen chloride. Molten diphenylamine reacts vigorously with cyanogen chloride. At temperatures below 250°, the main product of the reaction is tetraphenylguanidine; above 250°, a considerable quantity of polymeric diphenylcyanamide (m.p. 292°) forms. The latter is insoluble in water, alcohol, ether and benzene[49].

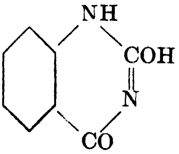
Meta-phenylenediamine reacts in aqueous solution with cyanogen bromide in the presence of sodium bicarbonate, forming *m*-phenylene-bis-cyanamide, prisms melting at 205–207° and turning to a solid soon after melting. Under the same conditions, *para-phenylenediamine* forms *p*-cyanamidophenylurea, needles which become blue on exposure to air, melt at 255°, and solidify soon after melting. The bis-cyanamido compound may be prepared from p-phenylenediamine under anhydrous conditions. *o*-Phenylenediamine, treated with an excess of cyanogen bromide, yields a mixture of *o*-phenyleneguanidine, $C_6H_4(NH)_2C{:}NH$, and iminodicarbonyl-*o*-phenyleneguanidine[47].

The hydrobromide of 2-amino-1,2-naphthimidazole,



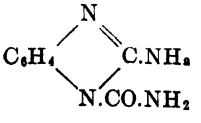
results from the reaction of 1,2-naphthalenediamine with an aqueous solution of cyanogen bromide. The free base melts at 212–215°[50].

Anthranilic acid reacts with cyanogen bromide in warm aqueous solution forming diphenylguanidinedi-*o*-carboxylic acid, $(COOH.C_6H_4NH)_2C{:}NH$. On boiling with concentrated hydrochloric acid, this compound is converted to benzoyleneurea,



and anthranilic acid[51].

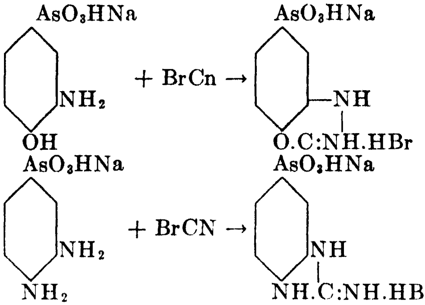
o-Aminophenylurea reacts with cyanogen bromide in aqueous solution forming *o*-cyanamidophenylurea, $CNNH.C_6H_4NH.CONH_2$. This compound is converted, on heating above 110° in the presence of water, to *o*-phenylene-α-guanylurea[52],



Cyanogen bromide reacts with *sodium para-arsanilate* in cold aqueous solution to form *p*-carbamidophenylarsinic acid:

$$NaHAsO_3.C_6H_4NH_2 + BrCN + H_2O \rightarrow H_2AsO_3.C_6H_4.NH.CO.NH_2 + NaBr$$

Other amino aryl arsinic acids react in a similar manner. If a hydroxy or a second amino group is present in the molecule in ortho position with respect to the amino group, condensation with the CN-group takes place between the cyanamido group and the hydroxy or amino group[53], thus:



Cyanogen bromide reacts with *cyanamide* forming melanuric acid. With sodium amide, cyanogen bromide forms sodium dicyanimide:

$$3NaNH_2 + 2BrCN \rightarrow NaN(CN)_2 + 2NaBr + 2NH_3$$

Sodium dicyanimide also results from the reaction of cyanogen bromide with sodium cyanamide in aqueous solution. Free dicyanimide, which is a very strong acid, tends to polymerize and has not been isolated in the pure form[115]. Cyanogen bromide reacts with the alkali metal salts of *substituted cyanamides* forming substituted dicyanimides:

$$R.NK.CN + BrCN \rightarrow RN(CN)_2 + KBr$$

The phenyl-, *o*- and *p*-tolyl-, *o*- and *p*-methoxyphenyl-, *p*-ethoxyphenyl-, 4-chloro-3-aminophenyl- and α-naphthyldicyanimides have been made[54]. The alkali metal salt of dicyanoguanidine results from the reaction of an alkali metal salt of dicyanodiamide and cyanogen chloride in anhydrous media[140].

Reaction of Cyanogen Halides with Tertiary Bases

Tertiary bases react with cyanogen bromide forming a disubstituted cyanamide and a hydrocarbon bromide:

$$R_1R_2NR_3 + BrCN \rightarrow R_1R_2N.CN + R_3Br$$

The reaction apparently proceeds in two stages, first a quaternary base forming by the addition of cyanogen bromide, this then decomposing to a halide and cyanamide. Aliphatic amines react readily, reaction being, in general, the more vigorous the smaller the radicals attached to nitrogen. Phenyl groups attached to nitrogen reduce the reactivity of the base. If two or more phenyl groups are attached to the nitrogen, the compound does not react with cyanogen bromide. When a phenyl group is introduced in place of a hydrogen in an aliphatic group, the reactivity of the tertiary base is reduced.

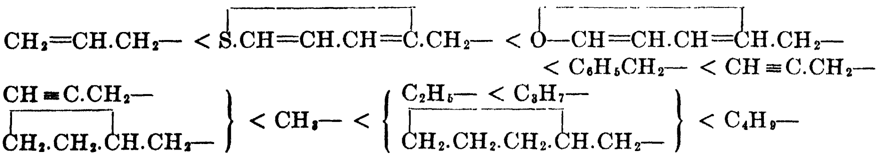
When unlike radicals are attached to nitrogen, then, as a rule, the smallest group is detached from the molecule. Thus, diethylmethylamine, reacting with cyanogen bromide, gives diethyl cyanamide and methyl bromide. This rule holds in the case of normal saturated aliphatic hydrocarbon radicals[55].

The allyl group is removed from the molecule in preference to the normal aliphatic saturated hydrocarbons. The propyl group is removed in preference to the isopropyl group[56]. The benzyl group is more readily removed than the groups benzyl, methyl, ethyl, propyl and phenyl; the allyl group is more readily detached than the benzyl group[57]. Methyl and ethyl groups are removed in preference to the phenyl group[64]. The α- and β-naphthyl groups are removed in preference to methyl groups, the α-naphthyl group in preference to the β-naphthyl group. The benzyl group is removed in preference to α- or β-naphthyl groups[58]. Other organic groups the ease of removal of which has been determined by Braun and co-workers[61] are given below. The group to the left of the sign of inequality is more readily removed than that to the right:

$$CH_2{=}CH.CH_2— < CH{\equiv}C.CH_2—$$

$$\left.\begin{array}{l}CH_3.CH{=}CH.CH_2—\\ C_6H_5.CH{=}CH.CH_2—\end{array}\right\} < CH_2{:}CH.CH_2$$

$$C_6H_{11}C{\equiv}C.CH_2— < CH{\equiv}C.CH_2—$$



$$CH_2{=}CH.CH_2— < \overline{S.CH{=}CH.CH{=}C}.CH_2— < \overline{O—CH{=}CH.CH{=}CH}.CH_2— < C_6H_5CH_2— < CH{\equiv}C.CH_2—$$

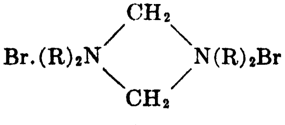
$$\left.\begin{array}{l}CH{\equiv}C.CH_2—\\ \overline{CH_2.CH_2.CH}.CH_2—\end{array}\right\} < CH_3— < \left\{\begin{array}{l}C_2H_5— < C_3H_7—\\ \overline{CH_2.CH_2.CH_2.CH}.CH_2—\end{array}\right\} < C_4H_9—$$

$$\left.\begin{array}{l}C_6H_5CH_2— < p\text{-}Cl.C_6H_4CH_2— < m\text{-}Cl.C_6H_4CH_2— < o.Cl.C_6H_4CH_2—\\ p\text{-}Cl.C_6H_4CH_2— < p\text{-}Br.C_6H_4CH_2— < p\text{-}IC_6H_4CH_2—\\ Cl—CH{=}CH—CH_2— < CH_2{=}CCl—CH_2—\\ BrCH{=}CH.CH_2— < CH_2{=}CBr.CH_2—\end{array}\right\} < CH_3—$$

$$p.C_6H_5—C_6H_4CH_2— < p\text{-}C_2H_5—C_6H_4CH_2— < p\text{-}CH_3C_6H_4CH_2— < C_6H_5—CH_2—$$
$$p\text{-}CH_2{=}CH.CH_2C_6H_4CH_2— < p\text{-}CH_3.CH{=}CH.CH_2C_6H_4CH_2— <$$
$$p\text{-}C_2H_5.CH{:}CH.CH_2C_6H_4CH_2— < p\text{-}C_6H_5CH{=}CH.CH_2C_6H_4CH_2—$$

The bond strength increases in the series, $C_6H_5(CH_2)_n—$, with increase in length of the aliphatic chain; the phenylethyl and phenylpropyl groups forming exceptions[60].

The bases, $(R)_2N.CH_2.N(R)_2$, which are readily obtained through the interaction of formaldehyde with secondary amines. $(R)_2NH$, react with cyanogen bromide to form the dialkyl cyanamides, $(R)_2NCN$, and methylene dibromide. The latter reacts with the unconverted methylenediamine, forming a compound of the probable structure,



which is unstable and decomposes in the presence of moisture to formaldehyde and the hydrobromide of the secondary amine[59].

β-Bromoallylmethylaniline, $CH_2{:}C(Br).CH_2N(CH_3)C_6H_5$, reacts with cyanogen bromide forming allylene bromide, $CH{\equiv}CH.CH_2Br$, and methylphenyl cyanamide[61].

The reaction with cyanogen bromide proceeds in two directions in the case of compounds that contain a methyl group to which CN— or —$COOC_2H_5$ is attached[62]:

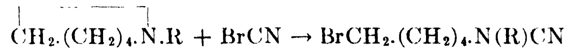
$$R_2NCH_2.CN + BrCn \rightarrow R_2N.CN + BrCH_2CN \text{ or } RN(CN).CH_2CN + R.Br$$

The aromatic aminoacetonitriles, such as $C_6H_5N(CH_3)CH_2CN$, are not cleaved by reaction with cyanogen bromide, but give the *para*brominated derivative of the aminonitrile[63], *p*-$BrC_6H_5N(CH_3)CH_2CN$.

The methyl group attached to nitrogen in morphine may be replaced by a CN-group by reaction with cyanogen bromide; apomorphine cannot thus be de-methylated.[65] Similarly, one of the two methyl groups, attached to nitrogen in the molecule of thebaine may be replaced by a CN-group[65,66]. Cyanonorhydroxycodeine has also been prepared by the same reaction[67]. Quinine treated with two moles of cyanogen bromide gives bromocyanoquinine, $C_{20}H_{24}O_2N_2.2BrCN$, needles softening at 95° and decomposing at a higher temperature[116]. Quinidine gives the bromocyanide $C_{20}H_{24}O_2N_2.2BrCN$, small needles decomposing at 118°; cinchonidine gives $C_{19}H_{22}ON_2.BrCN$, m.p. 107–108°[117].

Alkyl residues attached to nitrogen forming part of a ring may be exchanged by the CN-group by the action of cyanogen bromide. As in the case of other tertiary bases, this exchange takes place with varying degrees of ease, according to the character of the alkyl group attached to nitrogen. Alkyl groups having a double bond in the β-γ-position are readily detached, as are also the methyl and benzyl residues.

In most cases, a second reaction involving the rupture of the nitrogen ring also takes place:



$$CH_2.(CH_2)_4.N.R + BrCN \rightarrow BrCH_2.(CH_2)_4.N(R)CN$$

The resulting brominated compound reacts with the unconverted cyclic base to form a quaternary compound:

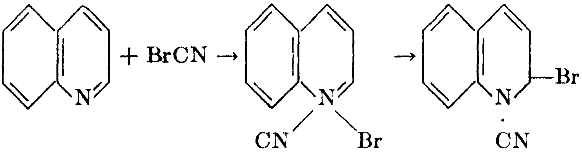
$$C_5H_{10}N.R + BrCH_2(CH_2)_4.N(R)CN \rightarrow C_5H_{10}N(R)(Br).(CH_2)_5N(R)CN$$

The two reactions take place simultaneously, though to varying extent, in the case of all N-substituted homologues of piperidine except those in which the groups attached to nitrogen are methyl, benzyl and allyl radicals; in the latter case, the radicals are detached but the piperidine ring is not broken. N-Substituted tetrahydroquinolines and dihydroindoles react in a similar manner[68]. N-Methyl-1-propyl-1,2-dihydroquinoline in dilute ethereal solution reacts vigorously with cyanogen bromide, ring fissure taking place, with the formation of the compound (1) $CN.N(CH_3)C_6H_4.CH{:}CHCH(Br).C_3H_7(2)$[118].

Cyanogen bromide reacts vigorously with N-methyl morpholine in ether solution; fissure of the ring occurs without demethylation and the resulting compound is $CH_3N(CN)(CH_2)_2O(CH_2)_2Br$[119]. The reaction of cyanogen bromide with N,N′-dimethylpiperazine yields methylvinylcyanamide $CH_3N(CN)CH{:}CH_2$, and 2-bromoethylmethylcyanamide $BrCH_2.CH_2N(CN)CH_3$.

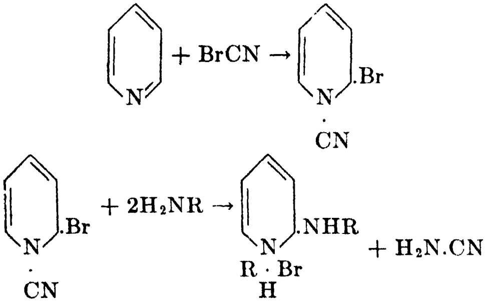
Crystalline addition products with cyanogen bromide have been obtained from brucine and dihydrobrucine. These are fairly stable compounds, not decomposed with water or alcohol and stable at 110°. Strychnine, dihydrostrychnine and strychnidine also form addition products with cyanogen bromide, but these are unstable and gradually decompose to cyanogen bromide and the alkaloid[69].

Cyanogen halides form unstable addition compounds with cyclic amines of the pyridine and quinoline type, which are transformed to α-halo-N-cyano compounds by intramolecular rearrangement[55,70,71]:



Cyanogen bromide and hydrocyanic acid reacting simultaneously with quinoline give 1,2-dicyano-1,2-dihydroquinoline; a similar reaction takes place with *iso*quinoline[104].

Cyanogen halides and primary or secondary bases reacting simultaneously with pyridine type bases form highly colored compounds. The reaction may be represented as follows:

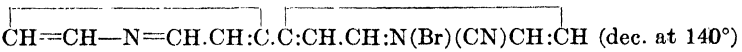


König[71] prepared a large number of derivatives of N-cyano-α-bromodihydropyridine by reaction with various bases. The colors of the compounds obtained were as follows:

Derivative	*Color*
o, *m*- and *p*-Toluidine	red
o-Xylidine	red
o- and *p*-Chloraniline	red
o-, *m*- and *p*-Nitroaniline	red
o-Anisidine	yellowish red
o-Aminophenol	rose red
Anthranilic acid	rose red
m- and *p*-Aminobenzoic acid	brown
p-Aminobenzaldehyde	red
p-Aminosalicylic acid	brown
o-, *m*- and *p*-Phenylenediamine	red
m-Toluenediamine	red
p-Aminodimethylaniline	violet

Derivative	*Color*
Ethylaniline	golden yellow
Benzylaniline	pure yellow
Dehydrothio-*p*-toluidine	red
Naphthionic acid	brownish red
2,6-Naphthylaminesulfonic acid	brownish red
Aminonaphthol	brown
2,5,7-Aminonaphtholsulfonic acid	violet red
2,8,6-Aminonaphtholsulfonic acid	violet
α, α'-Naphthalenediamine	brownish violet
Aminoazotoluol	heliotrope
Benzidine	lilac
Toluidine	reddish violet
Dianisidine	bluish violet

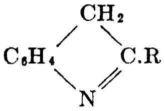
γ,γ'-Dipyridyl-N-monobromocyanide,



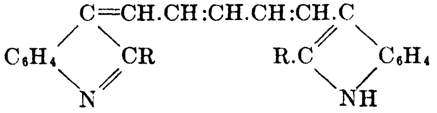
$\mathrm{CH{=}CH{-}N{=}CH.CH{:}C.C{:}CH.CH{:}N(Br)(CN)CH{:}CH}$ (dec. at 140°)

is obtained as a white precipitate by the interaction of cyanogen bromide and *dipyridyl* in alcoholic solution. This gives a deep red violet dye with aniline[72].

Bromocyanopyridine reacting with indols



forms the compounds



which are crystalline, basic dyes[103].

Cyanogen chloride or bromide react with *aminoanthraquinone* and its derivatives to form dyes varying in shade from gray-blue to black. These compounds are guanidine or *iso*melamine derivatives[73].

Reaction of Cyanogen Halides with Tertiary Arsines

Cyanogen bromide forms addition compounds with tertiary arsines. The resulting compounds decompose, as a rule, to an alkyl bromide and a dialkyl cyanoarsine[74].

Reaction of Cyanogen Halides with Alkali Metal Salts of Weak Acidic Compounds

The reaction of cyanogen halides and soluble salts of weakly acidic compounds is typified by that between cyanogen halides and soluble thiocarbamates[75]:

$$\mathrm{R_1R_2N.CS.SNa + ClCN \rightarrow R_1R_2NCS.SCN + NaCl}$$

The thiocyano group in the reaction product may be replaced by a phenylmercapto or phenoxy group:

$$R_1R_2N.CS.SCN + C_6H_5SH + NaOH \rightarrow R_1R_2NCS.SC_6H_5 + NaSCN$$
$$R_1R_2N.CS.SCN + C_6H_5OH + NaOH \rightarrow R_1R_2NCS.OC_6H_5 + NaSCN$$

Xanthates, thiophosphates, mercaptans and other thioacid salts also give the reaction.

Terpene thiocyanates, selenocyanates and tellurocyanates may be prepared from metal salts of the sulfide, selenide and telluride of terpene and cyanogen chloride[76].

Cyanopyrrole,

$$\overline{\mathrm{CH{:}CH.CH{:}CH.N}}\mathrm{.CN}\ (\text{m.p. } 210°)$$

has been obtained through the interaction of potassium pyrrole and cyanogen chloride[77].

Cyanogen chloride reacts with sodio ethyl acetoacetate, forming cyanoacetoacetic ethyl ester[78], $CH_3COCH(CN).COOC_2H_5$. Cyanomalonic ethyl ester, $CNCH.(COOC_2H_5)_2$, m.p. 37.5°, forms through the interaction of sodio malonic ethyl ester and cyanogen chloride[79]. Sodio benzyl cyanide reacts with cyanogen bromide, forming bromobenzyl cyanide[80]:

$$C_6H_5CH(Na)CN + BrCN \rightarrow C_6H_5CH(Br).CN + NaCN$$

Benzoyl cyanoacetic ethyl ester, $C_6H_5COCH(CN)COOC_2H_5$, m.p. 40°, results from the reaction of cyanogen chloride with sodium ethyl benzoyl acetate in absolute alcohol[121].

Cyanazide, m.p. 40.3°, has been prepared from sodium azide and cyanogen bromide[81]. The compound is a dimer[82].

Cyanogen Halides in Friedel-Crafts Reaction

Cyanogen chloride reacts with benzene and other aromatic hydrocarbons in the presence of aluminum chloride, forming a nitrile of the hydrocarbon[83]. Cyanogen bromide reacts in the same manner[84].

The reaction in general proceeds poorly and a considerable proportion of *sym*-trizole derivatives also form. These apparently result through the interaction of cyanuric halide, which first forms, with the hydrocarbons. Very little triazole derivative is obtained from anisole.

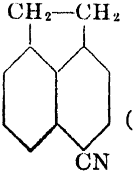
The cyanogen group enters the *p*-position with respect to alkyl groups, and if this position is occupied, reaction does not occur.

Karrer and Zeller[85] found that nearly quantitative yields of nitrile may be obtained with freshly prepared cyanogen bromide. These authors prepared benzonitrile, *p*-tolunitrile and 9-cyanoanthracene.

Benzonitrile was prepared as follows:

Twenty-five grams of finaly powdered anhydrous aluminum chloride were suspended in 150 cc of benzene and 15 grams of freshly prepared cyanogen bromide were added. The mixture was heated to boiling under a reflux condenser until the evolution of hydrobromic acid ceased. The liquid was then cooled, and ice was added. The benzene-benzonitrile layer was separated and fractionally distilled, the nitrile fraction distilling between 187–190°. The yield of pure benzonitrile was 10 grams.

The following nitriles have been prepared by this reaction[86]:
Acenaphthene nitrile,



(m.p. 112–113°)

α-thiophene nitrile, m.p. 194–195°; phenetol-4-nitrile, m.p. 61–62°; 1-ethoxy-4-cyanonaphthalene, m.p. 85°; 1-cyano-2-methoxynaphthalene, m.p. 94°; 1,2-dimethoxy-4-cyanobenzene; 1,3-dimethoxy-4-cyanobenzol, m.p. 89°; and hydroquinone dimethyl ether nitrile, m.p. 80°. Poor yields of nitrile were obtained from *m*-tert.-butyltoluene.

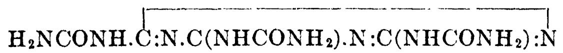
Miscellaneous Reactions of Cyanogen Halides

Organic sulfides react with cyanogen bromide, forming a thiocyanate and a bromide[87]:

$$o\text{-}CH_3.C_6H_4.S.C_6H_4.CH_3(\text{-}m) + BrCN \rightarrow o\text{-}CH_3.C_6H_4.SCN + m\text{-}CH_3.C_6H_4Br$$
$$o\text{-}CH_3.C_6H_4.S.C_6H_4.CH_3(p) + BrCN \rightarrow o\text{-}CH_3.C_6H_4.SCN + p\text{-}CH_3.C_6H_4.Br$$

On reacting cyanogen bromide with mixed aliphatic sulfides, the lighter radical combines with bromine. Thus methyl ethyl sulfide yields methyl bromide and ethyl thiocyanate; ethyl propyl sulfide gives ethyl bromide and propyl thiocyanate. Methyl benzyl sulfide yields benzyl bromide and methyl thiocyanate; allyl benzyl sulfide gives allyl bromide and benzyl thiocyanate.

Urea heated to 150° with cyanogen bromide in a sealed tube reacts to form the triureid of cyanuric acid,



$$H_2NCONH.C{:}N.C(NHCONH_2).N{:}C(NHCONH_2){:}N$$

an amorphous, insoluble powder which sublimes with decomposition when heated. It is soluble in strong acids and in aqueous caustic[122].

Cyanogen chloride, reacting with an aqueous alkaline solution of sodium sulfite, gives sodium cyanide, chloride and sulfate[123]. Cyanogen chloride is not reduced by sodium thiosulfate or hydriodic acid[124].

Cyanogen bromide is reduced by aqueous sulfurous acid quantitatively to hydrocyanic and hydrobromic acids. Hydriodic acid and hydrogen sulfide exert a similar reducing action on cyanogen bromide; with hydrogen sulfide, varying quantities of thiocyanic acid also result, alkalies promoting the formation of this compound[125]. Sodium thiosulfate also exerts a reducing action upon cyanogen bromide, the products resulting from the reaction being sodium cyanide, chloride, tetrathionate and other compounds[126]. Stannous chloride, arsenic sulfate, hydrazine sulfate, ferric sulfate, potassium thiocyanate, potassium nitrate and oxalic acid are without action on cyanogen bromide[124].

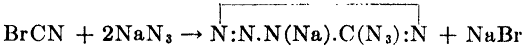
Cyanogen iodide is reduced by an aqueous solution of sulfur dioxide in excess to hydrocyanic acid and hydriodic acid; with a half molecular equivalent of sulfur dioxide, iodine and hydrocyanic acid are the products of the reaction. Other reducing agents react in a similar manner[127].

Thiocarbamide reacts with cyanogen bromide giving cyanamide and thiocyanic acid[88]:

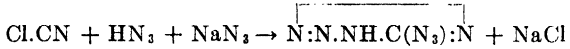
$$H_2N.CS.NH_2 + BrCN \rightarrow H_2N.CN + HSCN + HBr$$

Some carbon dioxide is also formed during the reaction. In the presence of a strong acid, hydrocyanic and hydrobromic acids and formamidine disulfide are formed.

Tetrazide and its salts have been prepared by the reaction of cyanogen halides and alkali or alkaline earth metal salts of hydrazoic acid[89]:

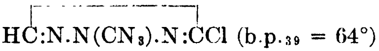


$$BrCN + 2NaN_3 \rightarrow N{:}N.N(Na).C(N_3){:}N + NaBr$$



$$Cl.CN + HN_3 + NaN_3 \rightarrow N{:}N.NH.C(N_3){:}N + NaCl$$

Diazomethane reacting with cyanogen chloride gives N-methyl-3-chloro-osotriazole,



$$HC{:}N.N(CN_3).N{:}CCl \text{ (b.p.}_{39} = 64°)$$

and a small amount of 3-chloroosotriazole. Cyanogen bromide gives in addition resinous products; cyanogen iodide does not react[102].

Methanol containing some water reacts vigorously with cyanogen chloride if the concentration of the latter is sufficiently high, giving methyl carbonate, $H_2NCOOCH_3$. No apparent reaction is observed if the concentration of cyanogen chloride is low[128]. Ethanol under similar conditions reacts on long standing in sunlight or on heating to 80° giving urethane, $H_2NCOOC_2H_5$, diethyl carbonate, and a little ethyl chloride[129].

Cyanogen chloride reacts with sodium ethoxide in alcoholic solution forming ethyl iminocarbonate[90]:

$$C_2H_5ONa + C_2H_5OH + ClCN \rightarrow HN{:}C(OC_2H_5)_2 + NaCl$$

This reaction takes place also with a concentrated alcoholic solution of sodium hydroxide:

$$2C_2H_5OH + NaOH + Cl.CN \rightarrow HN{:}CO(C_2H_5)_2 + NaCl + H_2O$$

Phenyl iminocarbonate, $HN{:}C(OC_6H_4)_2$, may also be prepared by this method. This compound may be converted to diphenyl carbonate by hydrolysis with dilute hydrochloric acid. Bis-(2-nitrophenyl) iminocarbonic ester, $HN{:}C(OC_6H_4NO_2)_2$, m.p. 124–125°, results from the interaction of cyanogen chloride and sodium *o*-nitrophenolate in aqueous solution. It is decomposed by alcohol or acetic acid, and on boiling with water, acids, and bases to nitrophenol, carbon dioxide and ammonia[130].

Iminocarbonates are generally unstable and change on standing to cyanuric acid esters:

$$3HN{:}C(OC_2H_5)_2 \rightarrow (C_2H_5OCN)_3 + 3C_2H_5OH$$

Cyanogen halides reacting with sodium alcoholates give alkyl cyanurates and not the monomeric isocyanates. Similarly, sodium phenolate reacting with cyanogen halides gives triphenyl cyanurate[91].

Ethyl cyaniminocarbonate results in 63% yield upon treating a solution of 10.5 grams of potassium cyanide, 28 grams of ethanol and 50 grams of water at 0° with 10 grams of cyanogen chloride[131]:

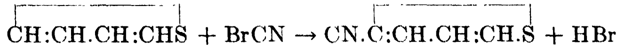
$$KCN + ClCN + C_2H_5OH \rightarrow CNC(:NH)OC_2H_5 + KCl$$

Cyanogen chloride is hydrolyzed by aqueous hydrochloric acid of a concentration greater than 18% with the formation of cyanic acid which is further hydrolyzed to carbon dioxide. Concentrated hydrochloric acid is without action on cyanogen iodide in the cold; on warming, the liquid assumes an orange color due to the formation of iodine chloride, ICl, which may be obtained in almost quantitative yield upon distillation[132]. Concentrated sulfuric acid causes the liberation of iodine from cyanogen iodide[133].

Cyanogen bromide combines with dry hydrogen chloride to form chloroforminobromide, BrCH:NCl[134].

Aqueous sulfur dioxide reduces cyanogen iodide to hydriodic acid and hydrocyanic acid. If cyanogen iodide is present in excess, some iodine is liberated. Alkali sulfites and other reducing agents also reduce cyanogen iodide in a similar manner[135]. Cyanogen iodide reacts with hydriodic acid with liberation of iodine; iodine is also formed through the interaction of cyanogen iodide with aqueous potassium iodide[136].

Cyanogen bromide reacts with thiophene, replacing an α-hydrogen with a CN-group:



$$CH{:}CH.CH{:}CHS + BrCN \rightarrow CN.C{:}CH.CH{:}CH.S + HBr$$

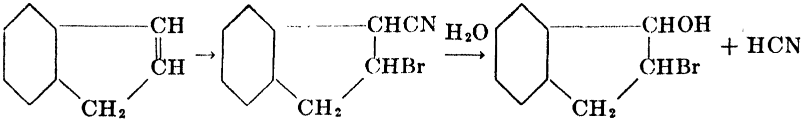
Cyanogen iodide resists the action of cold nitric and hydrochloric acids, but is decomposed by hot concentrated sulfuric acid. It is also decomposed by reducing agents but is not acted upon by oxidizing agents.

Attempts to cause cyanogen halides to react with ethylene have not met with success[92].

Cyanogen results on heating a mixture of cyanogen chloride and hydrocyanic acid at 300° in the presence of activated carbon[170]. A mixture of two moles of hydrocyanic acid with one of chlorine gives the same result. A virtually complete conversion is obtained at a space velocity of fifteen per hour at 650°.

Brominating Action of Cyanogen Bromide

Cyanogen bromide acts as a brominating agent toward a number of compounds. Benzene and naphthalene are brominated at 200°[93]. Phenol is brominated in the para-position at 130°; resorcinol is similarly brominated[94]. The aromatic group in aryl aminoacetonitriles is brominated in the para-position at the temperature of boiling water[95]. Acetoacetic ethyl ester is brominated by cyanogen bromide to $BrCH_2.COCH_2COOC_2H_5$; acetophenone is brominated in a similar manner. With indene an addition compound is obtained which is hydrolyzed to bromohydroxydihydroindene[96]:



Antipyrine is converted by cyanogen bromide to bromoantipyrine[137]; methylated imidazoles are converted to 3-bromoimidazoles, pilocarpine to 2-bromopilocarpine[138]. 1,2,4-Trimethoxybenzene is also largely brominated, as are other phenol ethers[139].

REACTIONS OF CYANAMIDE

Cyanamide, H_2NCN, the amide of cyanic acid, has assumed industrial importance as a basic chemical. It is the starting point in the manufacture of a number of products of great commercial importance. Its formation through the interaction of ammonia and cyanogen halides has been mentioned. It is made commercially in the form of the calcium compound from calcium carbide and nitrogen which react readily in the presence of certain promoters at a rapid rate and with evolution of heat in the neighborhood of 1200°.

The reactions of cyanamide as a nitrile have been discussed in the appropriate place in various chapters. In this section reactions related primarily to the amide group in cyanamide will be considered.

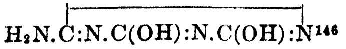
The presence of the strongly negative CN group in cyanamide imparts a mildly acidic character to the amido group, which is thus capable of forming metallic derivatives of the type MeNH.CN and $Me_2N.CN$. The acid character becomes further enhanced through the introduction of a second negative group. Thus dicyanimide $HN(CN)_2$ is a strong acid.

Calcium cyanamide CaNCN is not stable in contact with water, but is converted to the compound $Ca(NHCN)_2$ with formation of free lime. The disodium and dipotassium cyanamides also decompose in contact with water forming monosodium and monopotassium cyanamide. These mono-substituted salts are soluble in water. The di-alkali salts also decompose in contact with absolute methanol according to the equation[143],

$$NC\,CNa_2 + HOCH_3 \rightarrow NC\,CHNa + NaOCH_3$$

Cyanamide yields a dihydrochloride $CNNH_2.2HCl$ when a current of dry hydrogen chloride is passed through an absolute ethereal solution of the compound. Heated above 100°, the dihydrochloride decomposes into hydrogen chloride and mellon[144]. Substituted cyanamides do not, as a rule, react with hydrogen chloride, though a dihydrochloride has been obtained from dibenzyl cyanamide[145].

Treated with concentrated sulfuric acid cyanamide yields ammelide



$$H_2N.C{:}N.C(OH){:}N.C(OH){:}N$$[146]

Acetyl chloride reacts with cyanamide with violence in the absence of a diluent. The reaction proceeds smoothly when acetyl chloride is added slowly to an ethereal solution of cyanamide. The reaction is a complicated one, however, and only a small quantity of acetyl cyanamide can be isolated from the solution[147]. The sodium compound of acetyl cyanamide, $CH_3CON(Na)CN$, is prepared through the action of acetic anhydride upon monosodium cyanamide in absolute ether[148]. Other acid anhydrides react in the same manner. Sodium benzoyl cyanamide is similarly obtained from monosodium cyanamide and benzoyl chloride[149]:

$$2NaNHCN + C_6H_5COCl \rightarrow C_6H_5CON(Na)CN + H_2NCN + NaCl$$

Benzoyl cyanamide polymerizes on long heating to tribenzoylmelamine. Diacetyl cyanamide, $(CH_3CO)_2N.CN$, has been prepared through the interaction of the silver compound of acetyl cyanamide and acetyl chloride.

Ethyl chlorocarbonate, $ClCOOC_2H_5$, reacting with an ice-cooled aqueous solution of sodium cyanamide gives dicarbethoxy cyanamide, $CN.N(COOC_2H_5)_2$, m.p. 33°. The compound is hydrolyzed to diethyl allophanate, $H_2NCON(COOC_2H_5)_2$, when boiled with dilute hydrochloric acid[150].

Substituted chlorosulfonic acids, RSO_2Cl, react with monosodium cyanamide forming sulfone cyanamides[151]:

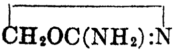
$$2NaHNCN + C_6H_5SO_2Cl \rightarrow C_6H_5SO_2N(Na)CN + H_2NCN + NaCl$$

Metallic cyanamides react with alkyl halides and other halogenated compounds to form substituted cyanamides. The reaction takes place most readily with compounds with a reactive halogen. Benzyl chloride reacts even with free cyanamide in absolute alcoholic solution giving dibenzyl cyanamide. In very dilute alcoholic solution *unsym.* dibenzyl urea is the product of the reaction.

1-Chloro-2, 4-dinitrobenzene reacts with cyanamide in aqueous or ethereal solution at room temperature with the formation of 2,4-dinitrophenyl cyanamide, m.p. 146–147° (dec.). Picryl chloride reacts similarly forming picryl cyanamide, m.p. 175–185° (dec.). The labile 5-nitro group in 2,4,5-trinitrotoluene may also be replaced by the cyanamido group by reaction with cyanamide, giving 3-methyl 4,6-dinitrophenyl cyanamide, m.p. 161–162°[152].

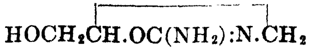
Allyl bromide reacting with disodium cyanamide gives diallyl cyanamide in 52 to 56% yield. When this compound is heated for six hours with sulfuric acid diallylamine is obtained in 80 to 86% yield[153].

The reaction of ethylene chlorohydrin with sodium cyanamide in aqueous solution apparently proceeds, not through the direct replacement of the chlorine by the cyanamido group, but rather through the formation first of ethylene oxide, which then reacts with the monosodium cyanamide in solution, the final reaction product being 2-aminoöxazoline,



$$CH_2OC(NH_2):N$$

The alkali required for the conversion of the chlorohydrin into oxide is derived through the interaction of disodium cyanamide with water. Glycerine mono- and dichlorohydrins react similarly yielding 5-methylol-2-aminoöxazoline



$$HOCH_2CH.OC(NH_2):N.CH_2$$

known facts, although a final proof that it truly represents the structure of the compound has not been obtained. The results of measurements of molecular refraction and absorption spectra indicate that the unsymmetrical formula correctly represents the structure of the molecule of cyanamide. There is evidence to support the assumption that the compound can undergo tautomeric change, and that the two forms co-exist in aqueous solution, the proportion of di-imine, HN:C:NH, increasing with dilution[169].

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Chapter 7

Replacement of Halogens or Other Acid Residues by the Nitrile Group: Other Reactions Involving Metallic Cyanides

Replacement of Sulfo, Sulfonic Groups and Halogens

Halogens and other acid residues in an organic molecule may be replaced by the nitrile group through the action of metallic cyanides:

$$R.X + NaCN \rightarrow R.CN + NaX$$

The ease with which this reaction proceeds depends upon the relative mobility of the halogen or the negative group, this in turn being determined by the nature of the compound of which it forms a part and the position of the negative residue in the molecule.

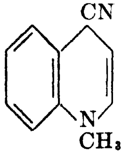
The halogen is replaced with great difficulty in certain types of compounds. In such cases, it is necessary to heat the halogenated compound with the metal cyanide at a comparatively high temperature for a long period. To this class of compounds belong many halogenated aliphatic hydrocarbons and, with very few exceptions, aromatic hydrocarbons in which the halogen is attached to a nuclear carbon atom. In these cases, the reaction is facilitated by the presence of a catalyst such as cuprous cyanide.

Replacement of Sulfo- and Sulfonic Groups. Aliphatic sulfates, being high boiling liquids, lend themselves to the convenient preparation of certain aliphatic nitriles. Thus, acetonitrile is obtained in good yield from methyl sulfate and aqueous sodium cyanide[1], the reaction proceeding in two stages:

$$(CH_3)_2SO_4 + NaCN \rightarrow CH_3CN + NaCH_3SO_4$$
$$Na(CH_3)SO_4 + NaCN \rightarrow CH_3CN + Na_2SO_4$$

The first takes place at ordinary temperature with a 92% yield, while the second proceeds to completion at about 85°. Propionitrile is similarly obtained from ethyl sulfate and an alkali cyanide but with a lower yield. It is necessary to heat the reaction mixture at red heat in the final stages.

Quinoline forms an addition compound with dimethyl sulfate; reacting with potassium cyanide, this gives N-methylcyano-4-quinoline[125],



Similarly N-methylbenzylcyanoacridane is obtained through the interaction of potassium cyanide and the addition product of benzylacridine and dimethyl sulfate[126].

Nitriles are obtained by fusing the alkali metal salt of an aromatic sulfonic acid with an alkali cyanide or ferrocyanide. The reactants should be completely dry and should be mixed intimately. For best results a 100% excess of cyanide should be used.

Monocyanonaphthalenes have been prepared from alkali salts of naphthalenesulfonic acids and potassium cyanide by strongly heating a mixture of these compounds[2]. Better yields are obtained by using potassium ferrocyanide in place of potassium cyanide[3].

Wahl and co-workers[4] obtained a 30% yield of α-cyanonaphthalene (m.p. 35–36°) and a 22% yield of β-cyanonaphthalene (m.p. 66°) by this method.

Nicotinonitrile may be prepared from sodium pyridine-3-sulfonate by fusion with sodium cyanide. Pyridine-3-sulfonic acid may be obtained directly from pyridine[5].

β-Cyano-γ-picoline has been obtained in 23 to 33% yield by fusing sodium γ-picoline-β-sulfonate with a 5 to 1 mixture of sodium- and potassium cyanides[142].

Heated with sodium cyanide, sodium benzene sulfonate reacts to form benzonitrile in 33% yield[7].

With salts of naphthalenedisulfonic acids, alkali cyanides yield dinitriles of naphthalene. Thus, dicyanocompounds have been obtained from 2:7-, 1:7-, 2:6-, and 1:5-disulfonates or cyanosulfonates, by distilling mixtures of these with potassium cyanide.

Bradbrook and Linstead[8] prepared dicyanonaphthalenes from the monocyanosulfonates by fusion with cyanides. The melting points of the nitriles and the yields were as follows:

Isomer*	1:2	2:1	1:3	1:4	1:5	1:6	1:7	1:8	2:6	2:7
M.P. °C	190	179	208	263	211	167	232	251	293	267
% Yield	75	76	17	71	53	18	31	9	42	8

References to the transformation of various additional aromatic sulfonic compounds to nitriles are given in the following tables:

Nitriles Obtained by Reaction of Potassium Sulfonates with Potassium Cyanide

Sulfonate	*Reference*
Benzenesulfonate	Merz, Z. *Chem.*, **4**, 33, 396 (1868)
3-Chlorobenzenesulfonate	Meyer and Stüber, *Ann.*, **165**, 166 (1873)
3-Bromobenzene sulfonate	Limpricht, *Ann.*, **180**, 92 (1875)
4-Chloro- and 4-bromobenzenesulfonate	Nölting, *Ber.*, **8**, 1113 (1875); Ireland, *Z. Chem.*, 164 (1869)
m-Nitrobenzenesulfonate	Fittig, and Ramsey, *Ann.*, **168**, 246 (1873)
o- and *p*-Toluenesulfonate	Paterno and Spica, *Gazz. chim. ital.*, **5**, 26 (1875); *Ber.*, **8**, 441 (1875)

* The first number indicates position of CN.

Sulfonate	*Reference*
p-Cymenesulfonate	Paterno and Fileti, *Gazz. chim. ital*, **5**, 30 (1875); *Ber.*, **8**, 442 (1875)
Diphenyl-4-sulfonate	Doebner, *Ann.*, **172**, 111 (1874)
Benzene-*m*-disulfonate	Nölting, *Ber.*, **8**, 1113 (1875); Borth and Sanhofer, *Ann.*, **174**, 236 (1874); *Ber.*, **8**, 1481 (1875); Korner and Monselise, *Gazz. chim. ital.*, **6**, 139 (1876); Meyer and Michler, *Ber*, **8**, 683 (1875)
Benzene-1,4-disulfonate	Nölting, *Ber.*, **8**, 1113 (1875); Korner, and Monselise, *Ber.*, **9**, 584 (1876); Garrick and Fittig, *Ann.*, **174**, 124 (1874)
Naphthalene-2,7-disulfonate	Ebert and Merz, *Ber.*, **9**, 604 (1876)
Naphthalene-2,6-disulfonate	Ebert and Merz, *Ber.*, **9**, 604 (1876)
Diphenyl-4,4′-disulfonate	Doebner, Ann., **172**, 116 (1874)
Pyrenedisulfonate	Goldschmidt and Wegscheider, *Monatsh*, **4**, 242 (1883)
Benzenetrisulfonate	Jackson and Wing, *Am. Chem. J.*, **9**, 329 (1887)

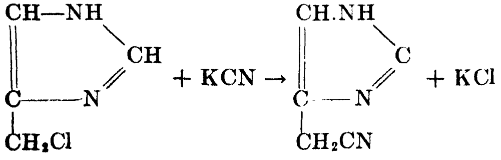
Nitriles Obtained by Reaction of Potassium Sulfonates with Potassium Ferrocyanide

Sulfonate	*References*
Benzenesulfonate	Witt, *Ber.*, **6**, 448 (1873)
Diphenyl-4-sulfonate	Rassow, *Ann.*, **282**, 142 (1894)
1-Phenanthrenesulfonate	Fieser, *J. Am. Chem. Soc.*, **54**, 4110 (1932)
2-Phenanthrenesulfonate	Werner and Ney, *Ann.*, **321**, 328 (1902)
3-Phenanthrenesulfonate	Werner and Ney, *Ann.*, **321**, 328 (1902); Japp and Schultz, *Ber.*, **10**, 1661 (1877); Schultz, *Ann.*, **196**, 13 (1879); Werner and Kunz, *Ann.*, **321**, 323 (1902)
9-Phenanthrenesulfonate	Werner and Kunz, *Ann.*, **321**, 323 (1902); Japp, *J. Chem. Soc.*, **37**, 83 (1880)
Acenaphthene-3-sulfonate	Oliveri-Mandalo, *Atti accad. Lincei*, (5) **21**, I, 779 (1912)

Replacement of Halogens. It is of advantage to use a solvent of relatively low volatility in preparing nitriles from halogenated hydrocarbons. Thus, ethyl chloride in alcoholic solution may be converted to ethyl cyanide in good yield at 100–105°[9]. Other aliphatic nitriles such as normal valeronitrile, methylsuccinonitrile, normal pimelonitrile and tricarballilic nitrile[10] have been prepared from the aqueous alcoholic solutions of the chlorides.

Succinonitrile may be obtained in 90–98% yield through the interaction of an alcoholic solution of ethylene dichloride with an alkali metal cyanide[11]. When ethylidine bromide, $CH_3.CHBr_2$, is heated with potassium cyanide, succinonitrile results instead of the expected methylmalononitrile.

Potassium cyanide reacts with chloromethylimidazole to form cyanomethylimidazole:



4-Chloro-1,2-butadiene reacts with sodium cyanide to give 4-cyanobutadiene[12], which polymerizes twenty times as fast as isoprene.

Cuprous cyanide reacting with crotyl- or methylvinylcarbinyl halides, $CH_3.CH:CH.CH_2X$, $CH_3CHX.CH:CH_2$, gives a mixture of isomeric nitriles consisting of about 92% 3-pentenenitrile and 8% 2-methyl-3-butenenitrile[127].

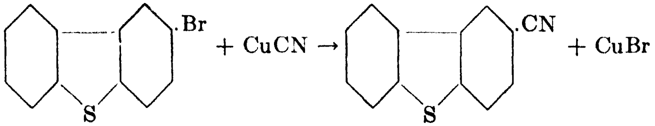
Rosenmund and Struck[13] prepared benzoic, terephthalic and aminobenzoic acids through the interaction of the appropriate halogen-substituted aromatic compounds and potassium cyanide in aqueous or aqueous alcoholic solution in the presence of cuprous cyanide in an autoclave at 200°, the nitriles formed being subsequently hydrolyzed to the corresponding acids. Halogenated naphthalene and thiophene derivatives also react with cuprous cyanide under the same conditions giving the corresponding cyano compounds.

Newman[14] obtained a 92–93% yield of 1-naphthonitrile by heating 1-chloro- or bromonaphthalene with CuCN in pyridine at 220 to 250°.

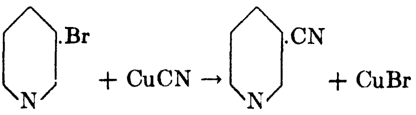
The reaction between aromatic bromine- and other halogen compounds and cuprous cyanide (*R. von Braun Nitrile Synthesis*) is autocatalytic, as shown by the fact that the rate of transformation of the halide to nitrile increases rapidly with time.

The order of increasing reactivity of various substituted brominated compounds was found by Koelsch and Whitney[15] to be as follows: p-$Ph_2CH.C_6H_4Br$, m-$Me.C_6H_4Br$, p-$PhCO.C_6H_4Br$, o-MeC_6H_4Br, Ph.Br, 1,3,5-$Me_3C_6H_2Br$, 1-$C_{10}H_7Br$, p-BrC_6H_4COOH.

2-Cyanodibenzothiophene has been obtained by heating 2-bromodibenzothiophene with cuprous cyanide at 240 to 270° for six hours[16]:



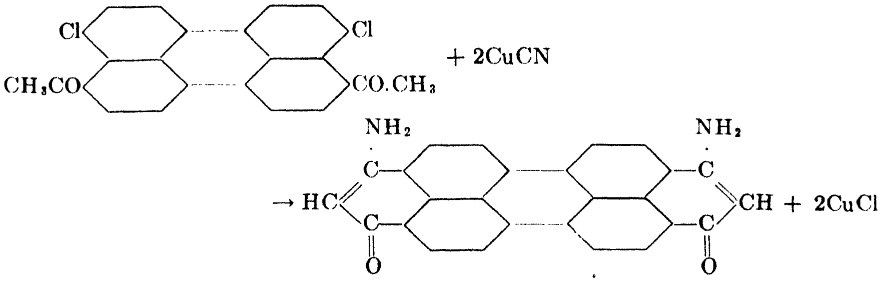
Nicotinonitrile has been prepared in a 50% yield from 3-bromopyridine and CuCN[19]:



o-Cyanoacetophenone has been obtained in 20% yield by heating a mixture of cuprous cyanide and o-chloroacetophenone in quinoline solution at 150°. The compound has been obtained in 80% yield from o-bromoacetophenone in pyridine solution at 120°. The low yield in the case of the chloro compound is explained by the formation of a tetrabenzoporphin-copper complex[20].

1,8-Dicyanoanthraquinone has been made by heating 1,8-dichloroanthraquinone with cuprous cyanide at 230°[128].

The interaction of cuprous cyanide and perihaloacylperylenes leads to the formation of dyes resulting from cyclization of the cyano and keto groups[21]:



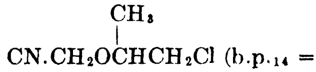
Alkyloxyacetonitriles have been prepared in good yields from chloromethyl ethers and cuprous cyanide:

$$ROCH_2Cl + CuCN \rightarrow ROCH_2.CN + CuCl$$

Bruson and McCleary[17] have prepared the following compounds by this reaction:

sec. Octyloxyacetonitrile, colorless oil	$b.p._{13}$	= 111–113°
2-Ethylhexyloxyacetonitrile	$b.p._{10}$	= 108–111°
Dodecyloxyacetonitrile	$b.p._{5}$	= 150–155°
Oleyloxyacetonitrile	$b.p._{3}$	= 198–203°
Cetyloxyacetonitrile	$b.p._{7}$	= about 215–220°
*Iso*undecyloxyacetonitrile	$b.p._{6}$	= about 122–126°

Spurlock and Henze[18] have similarly prepared β-chloroisopropoxyacetonitrile



$$CN.CH_2O\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Cl \ (b.p._{14} = 98\text{–}99°)$$

Slebodzinski[22] investigated the reaction of various halogenated aromatic compounds in alcoholic solution with potassium cyanide, in the presence of nickelous cyanide as a catalyst under 58–60 atm. pressure. The yields of the corresponding carboxylic acids obtained from the various compounds were as follows:

	%		%
C_6H_5I	72.5	*m*-$CH_3C_6H_4I$	32.0
o-$CH_3C_6H_4Cl$	7.44	*p*-$CH_3C_6H_4I$	32.0
m-$CH_3C_6H_4Cl$	4.6	*p*-$C_6H_4Cl_2$	12.4
o-$CH_3C_6H_4Br$	15.1	*m*-$COOH.C_6H_4I$	99.4
m-$CH_3C_6H_4Br$	6.3	*p,p*'-$Br_2(C_6H_4)_2$	5.1
o-$CH_3C_6H_4.I$	35.2	α-$C_{10}H_7Br$	20.0

The presence of certain groups in the vicinity of the carbon atom to which the halogen atom is attached causes an increase in the reactivity of halogen. Thus, phenyl and naphthyl groups attached to the carbon atom to which the halogen is attached cause an increase in the reactivity of the halogen. A similar effect is exerted by groups in which carbinol or carbonyl is present.

The chlorine in benzyl chloride is readily replaced with a nitrile group. Thus, benzyl cyanide may be obtained in an 80% yield by heating to boiling a suspension of potassium cyanide in benzyl chloride for 4 hours. Substituted benzyl chlorides act similarly. Thus, *o*-methoxybenzylcyanide is obtained readily by heating an alcoholic solution of *o*-methoxybenzyl chloride and sodium cyanide, some *o*-methoxybenzyl ethoxide also forming[23]:

$$CH_3OC_6H_4CH_2Cl + NaCN \rightarrow CH_3OC_6H_4CH_2CN + NaCl$$
$$CH_3OC_6H_4CH_2Cl + NaCN + HOC_2H_5 \rightarrow CH_3OC_6H_4CH_2OC_2H_5 + NaCl + HCN$$

Paty[24] prepared 5-bromo-2-methoxyphenylacetonitrile in 96% yield from 5-bromo-2-methoxybenzyl chloride and an aqueous alcoholic solution of potassium cyanide.

ω-Chlorobenzylidine aniline reacts with potassium cyanide to form the corresponding cyanide[25]:

$$C_6H_5CCl = N.C_6H_5 + KCN \rightarrow C_6H_5C(CN) = N.C_6H_5 + KCl$$

Other ω-chlorobenzylidines react in a similar manner forming compounds of the type $C_6H_5C(CN){:}N.R$. Compounds in which R is $C_6H_5CH_3$-*o*,*p*, and *m*, C_6H_5-NO_2-*o*, *m*, and CH_3 have been prepared[26].

Braun[27] prepared *γ-phenylpropyl cyanide* in 50% yield from the corresponding chloride; *ε-phenylcaproic nitrile* in 90% yield and 6-phenyloenantylic *nitrile* in 95% yield also from the corresponding iodides.

A naphthyl group attached to a methyl group activates halogens attached to this group. Thus, *naphthylacetonitriles* may be obtained from naphthylmethyl chlorides in good yield by heating the compounds with an aqueous alcoholic solution of an alkali cyanide:

$$C_{10}H_7CH_2Cl + NaCN \rightarrow C_{10}H_7CH_2CN + NaCl$$

Activation is even more pronounced if the naphthyl group contains an alkoxy group in the 2 position. Thus, 2-methoxynaphthylacetonitrile forms with great ease from 2-methoxynaphthylmethyl chloride, in cold aqueous acetone solution[28]:

$$CH_3OC_{10}H_6CH_2Cl + KCN \rightarrow CH_3OC_{10}H_6CH_2CN + KCl$$

Ethylene chlorohydrin reacts readily with alkali cyanides in aqueous solution to form ethylenecyanohydrin:

$$HO.CH_2.CH_2Cl + NaCN \rightarrow HOCH_2.CH_2CN + NaCl$$

Similarly α-aminopropylene-α-chlorohydrin gives γ-amino-β-hydroxypropionitrile[29]:

$$R.NH.CH_2CH(OH).CH_2Cl + NaCN \rightarrow RNH.CH_2C.H(OH).CH_2CN + NaCl$$

Glycerine chlorohydrin reacts very vigorously with aqueous sodium cyanide to form the corresponding nitrile[30]:

$$CH_2(OH).CH(OH)CH_2Cl + NaCN \rightarrow CH_2(OH)CH(OH).CH_2CN + NaCl$$

Lewisite II or β,β′-dichlorodivinylchloroarsine reacts to form β,β′-dichlorodivinylcyanoarsine[31]:

$$(Cl.CH{=}CH)_2.AsCl + NaCN \rightarrow (Cl.CH{=}CH)_2.AsCN + NaCl$$

Monochloroacetone reacts with potassium cyanide in alcoholic solution to form cyanoacetone[32], $CNCH_2COCH_3$.

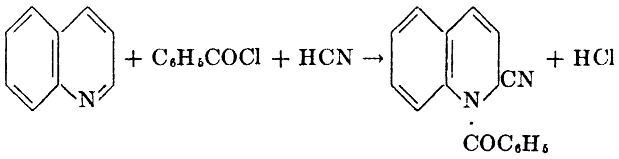
Bromoacetic ethyl ester reacting with potassium cyanide forms ethyl cyanoacetate and diethyl cyanosuccinate. Chloroacetic ethyl ester reacts in a similar manner. α-Chloro- and α-bromopropionic acid esters give α-cyanopropionic ethyl ester, diethyl dimethylcyanosuccinate, $C_2H_5OCOC(CN)(CH_3)CH(CH_3)$-$COOC_2H_5$, and $CH_3CH[C\ (:NH)\ CN].COOC_2H_5$. Ethyl α-bromobutyrate forms ethyl α-cyanobutyrate and diethyl diethylcyanosuccinate, $C_2H_5OCO.C(CN)$-$(C_2H_5).CH(C_2H_5).COOC_2H_5$[131].

Chloropicrin reacts with potassium cyanide in aqueous-alcoholic solution to form chloronitromalononitrile[132], $NO_2CCl(CN)_2$.

Benzoyl cyanide is obtained through the interaction of an alkali cyanide and benzoyl chloride:

$$C_6H_5.COCl + NaCN \rightarrow C_6H_5COCN + NaCl$$

bis-benzoyl cyanide forming simultaneously. The reaction also takes place readily with hydrocyanic acid in the presence of a base such as pyridine[33]. When quinoline[34] is used, 1-benzoyl-1-cyano-1,2-dihydroquinoline (Reissert's Compound) is formed in addition to benzoyl cyanide:



Acetyl chloride reacts with potassium cyanide to form pyruvic nitrile:

$$CH_3CO.Cl + KCN \rightarrow CH_3CO.CN + KCl$$

Sodium hydroxide decomposes acetyl cyanide to sodium acetate and sodium cyanide:

$$CH_3COCN + 2NaOH \rightarrow CH_3COONa + NaCN + H_2O$$

Ammonia reacts with benzoyl cyanide to form benzamide and ammonium cyanide, a reaction similar to the formation of urethane from ethyl cyanocarbonate and ammonia.

Mauthner[35] prepared the following acid cyanides from the corresponding acid chlorides:

	M.P. °*C*
p-Methoxybenzoyl cyanide	63–64
m-Methoxybenzoyl cyanide	111–112
3,4-Dimethoxybenzyol cyanide	116–117
2,5-Dimethoxybenzoyl cyanide	97–98
2,3,4-Trimethoxybenzoyl cyanide	89–90
3,4,5-Trimethoxybenzoyl cyanide	b.p.$_{14}$ 178–179

Acid cyanides RCOCN have been obtained in good yield from acid bromides, RCOBr, and cuprous cyanide. Acetyl cyanide, b.p. 93°, isobutyryl cyanide, b.p. 116–118°, and isovaleroyl cyanide, b.p. 145–149°, have been obtained by this method in yields of 85–87, 60 and 78% respectively. Propionyl cyanide, b.p. 108–110° has also been prepared by this method[133].

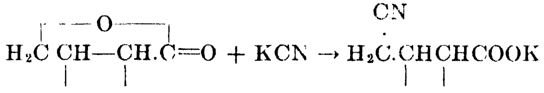
Phthalyl cyanide has been prepared by the interaction of phthalyl chloride and hydrocyanic acid in the presence of pyridine; isophthalyl and terephthaly cyanides have also been made by this method[134].

Diphenylcarbamyl chloride, $(C_6H_5)_2NCOCl$, heated with potassium cyanide at 180–200° gives diphenylcarbamyl cyanide, $(C_6H_5)_2N.COCN$, from which an amidoxime (m.p. 222.5°) and a thioamide, $(C_6H_5)_2NCOCSNH_2$, m.p. 220°, have been made[135].

ω-Cyanoacetophenone, $C_6H_5COCH_2CN$, has been obtained in 60% yield from ω-bromoacetophenone by reaction with potassium cyanide in alcoholic solution[36]. The compound is reduced by sodium amalgam and alcohol to $C_6H_5CH(OH).CH_2CN$.

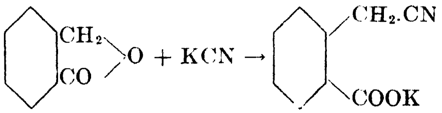
Chlorodiamylamine, $(C_5H_{11})_2NCl$, reacts with potassium cyanide in aqueous alcoholic solution forming diamyl cyanamide. Dibutyl cyanamide forms in a similar manner from chlorodiisobutylamine and potassium cyanide[37].

Reaction of Alkali Cyanides with γ-Lactones. The reaction of certain γ-lactones with alkali cyanides in the absence of a solvent at elevated temperatures presents a special case of the replacement of negative groups with a nitrile group[38]:

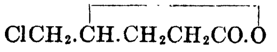


$$\mathrm{H_2C\ CH{-}CH.C{=}O + KCN \rightarrow H_2C.\overset{CN}{C}HCHCOOK}$$

Thus, the potassium salt of homophthalomonitrile forms with phthalide at 180°:



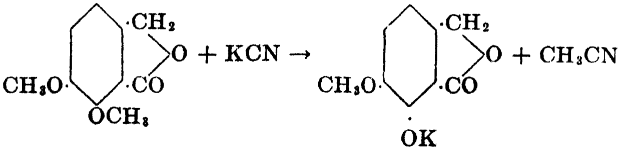
Completion of reaction is indicated by the rapid setting of the heated mass; heating must not be continued beyond this point, otherwise the compound reacts to form a condensation product. γ-Cyanovaleric acid may be prepared similarly from valerolactone and potassium cyanide by heating a mixture of equivalent quantities of these compounds in a sealed tube at 280–290° for three to five hours. With δ-chlorovalerolactone,



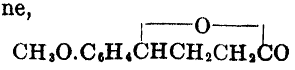
$$\mathrm{ClCH_2.CH.CH_2CH_2CO.O}$$

the reaction takes place at the boiling point of the compound[39]. The cyano group in these compounds is readily hydrolyzed to a carboxylic group.

Meconine does not give this reaction, but reacts as follows[40]:



γ-Anisyl-γ-butyrolactone,

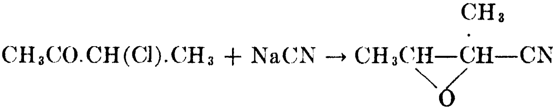


$$\mathrm{CH_3O.C_6H_4CHCH_2CH_2CO}$$

reacts with potassium cyanide at 210° forming the potassium salt of γ-anisyl-β-cyanobutyric acid, $CH_3OC_6H_4.CH_2CH(CN)CH_2.COOK$. The free cyano acid (m.p. 116.5°) may be cyclyzed by heating for one hour withh ydrogen fluoride to 6-methoxy-4-keto-1,2,3,4-tetrahydro-2-naphthamide, m.p. 178°[129].

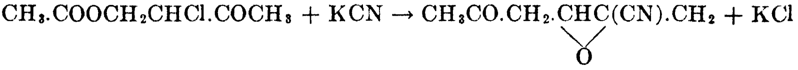
Replacements Involving Other Simultaneous Changes

Replacement of the halogen by a cyano group is accompanied in the case of certain compounds by other changes. The reaction of α-chloroethyl methyl ketone with sodium cyanide leads to the formation of an epoxy cyanide[141]:



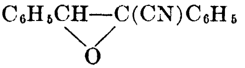
$$CH_3CO.CH(Cl).CH_3 + NaCN \rightarrow \underset{\diagdown\,O\,\diagup}{CH_3CH{-}\overset{CH_3}{C}H}{-}CN$$

According to Gerbaux[42], two isomers are formed, one boiling at 155 to 156° and the other at 142 to 143° under 758 mm pressure, the former in a 35% yield, the latter in 65% yield. α-Halogenated ketones in general react in a similar manner. Thus, ethyl α-chloroacetylacetate reacts with potassium cyanide to form an epoxy nitrile[43]:



$$CH_3.COOCH_2CHCl.COCH_3 + KCN \rightarrow CH_3CO.CH_2.\underset{\diagdown\,O\,\diagup}{CHC(CN).CH_2} + KCl$$

1-Chloro-1,2-diphenylethanol, reacting with potassium cyanide, gives 1-chloro-2-cyano-1,2-diphenylethanol, and this changes to 1-cyano-1,2-epoxydiphenylethane[136],



$$\underset{\diagdown\,O\,\diagup}{C_6H_5CH{-}C(CN)C_6H_5}$$

This compound is also obtained by the reaction of potassium cyanide and desyle chloride[137], $C_6H_5CHCl.COC_6H_5$. Phenylchloroacetone, $C_6H_5CHCl.COCH_3$, reacting with potassium cyanide gives 2-methyl-3-phenyl-2,3-epoxypropionitrile[138].

Chloropropyl alcohol, $CH_3CHCl.CH_2OH$, reacting with potassium cyanide forms cyanoisopropyl alcohol[139], $CNCH_2CH(OH)CH_3$.

β-Ethoxypropionitrile, $CH_3CH(OC_2H_5).CH_2.CN$, and pyrotartaric nitrile, $CH_3CH(CN).CH_2CN$, have been obtained through the action of potassium cyanide on an alcoholic solution of allyl iodide[44].

Potassium cyanide reacts with diethyl monochloromaleate to form *potassium dicyanosuccinate*[45], $KOCO.CH(CN).CH(CN)COOK$. One nitrile group in this compound may be hydrolyzed to carboxyl.

Potassium cyanide reacts with dichloroglycid, $ClCH_2.CCl = CH_2$, to form *tricarballylonitrile*, $CH_2(CN).CH(CN).CH_2CN$. If a deficiency of cyanide is used, *β-chlorocrotonic nitrile* forms, which, on hydrolysis with alkali gives hydroxycrotonic acid[46].

Claus and, independently, Bourgoin[47] showed that chloroform and carbon dioxide are products of the reaction of potassium cyanide and potassium trichloroacetate. The chlorine atoms in dichloroacetic ethyl ester are not replaceable by nitrile groups by reaction with potassium cyanide[48].

Potassium cyanide reacts with 1,2-dichlorodibromoethane to form α,β-dichloro-α-bromoethylene[49]:

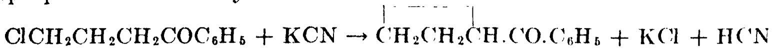
$$ClBrCH.CHBrCl + KCN \rightarrow ClBrC{:}CHCl + KBr + HCN$$

A similar reaction takes place with 2,4-dibromo-2,4-dimethylpentane, resulting in the formation of 2,4-dimethylpentene-(1)-ol-(4)[50]:

$$(CH_3)_2CBr.CH_2.CBr.(CH_3)_2 + 2KCN + H_2O \rightarrow (CH_3)_2C(OH).CH_2.C({:}CH_2).CH_3 + 2KBr + 2HCN$$

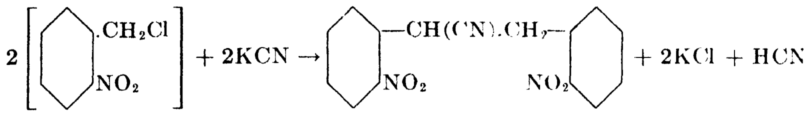
3-Chloro-1,2-butene, $CH_3CHCl.CH{:}CH_2$, heated with cuprous cyanide at 60 to 70° for one and a half hours gives a large proportion of $CH_3CH{:}CH.CH_2CN$.[127]

Potassium cyanide reacts with γ-chlorobutyrophenone to form benzoylcyclopropane in excellent yield[51]:

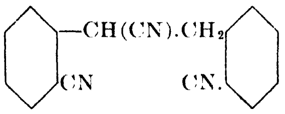


$$ClCH_2CH_2CH_2COC_6H_5 + KCN \rightarrow \underbrace{CH_2CH_2CH}.CO.C_6H_5 + KCl + HCN$$

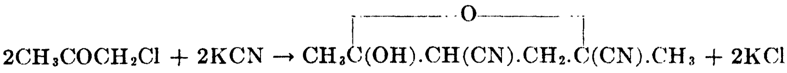
o-Nitrobenzyl chloride gives in addition to *o-nitrobenzyl cyanide*, some *o-dinitrocyanodibenzyl*[52]:



Similarly, *o*-cyanobenzyl chloride forms *tricyanodibenzyl*[53]:

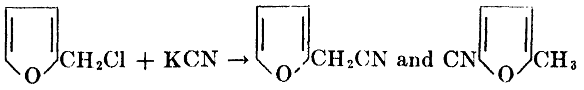


Monochloroacetone reacts with potassium cyanide in aqueous solution to form 2,5-dimethyl-5-hydroxytetrahydrofurane-2,4-dinitrile[54]:

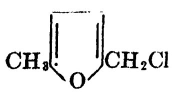


$$2CH_3COCH_2Cl + 2KCN \rightarrow CH_3C(OH).CH(CN).CH_2.C(CN).CH_3 + 2KCl$$

Furfuryl chloride gives *furfuryl cyanide* and *2-methyl-5-cyanofurane:*

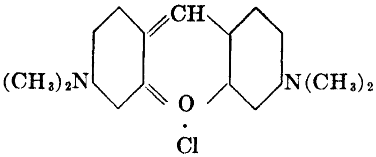


5-Methylfuryl chloride,

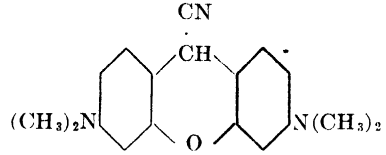


gives only the normal reaction product 5-*methylfuryl cyanide*[55].

Dimethyl-9,10-acridine chloride reacting with potassium cyanide gives dimethyl-9,10-cyano-9′-acridane[140]. A similar transformation is observed in the case of the compound,

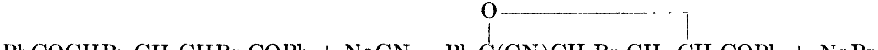


which gives tetramethyldiaminocyanoxanthen,



the oxomium cyanide first formed being unstable above 75°[141].

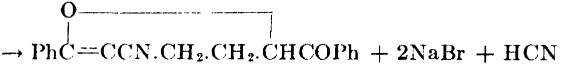
1,3-Dibromo-1,3-dibenzoylpropane reacts with sodium cyanide in aqueous solution to form a mixture of the four theoretically possible 2-cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofuranes[56]:



$$\mathrm{PhCOCHBr.CH_2CHBr.COPh + NaCN \rightarrow Ph\,\overset{O}{C}(CN)CH.Br.CH_2.\overset{|}{C}H.COPh + NaBr}$$

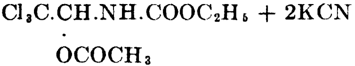
1,4-Dibrom-1,4-dibenzoylbutane gives a *cyanodihydropyran* derivative[57]:

PhCO.CHBr.CH$_2$CH$_2$CHBr.COPh + 2NaCN



$$\mathrm{\rightarrow Ph\overset{O}{C}{=}CCN.CH_2.CH_2.\overset{|}{C}HCOPh + 2NaBr + HCN}$$

Acetylchloral urethane reacts with potassium cyanide to form *ethyl dichlorocyanovinylcarbamate*[58]:



$$\mathrm{Cl_3C.\underset{OCOCH_3}{CH}.NH.COOC_2H_5 + 2KCN}$$

$$\mathrm{\rightarrow Cl_2C{:}C(CN).NH.COOC_2H_5 + HCN + KCl + CH_3COOK.}$$

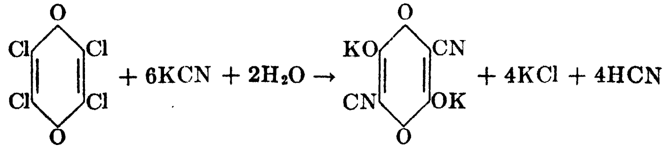
α-Chlorochloralamides form *β,β-dichloro-α-cyanovinyl* derivatives[59]:

$$\mathrm{R.CONH.CHCl.CCl_3 + 2KCN \rightarrow RCO.NH.C(CN){:}CCl_2 + KCl + HCN}$$

Chalkone dibromides react with potassium cyanide in warm alcoholic solution to form *β-aroyl-α-arylpropionitriles*[60]:

$$\mathrm{R_1COCHBr.CHBr.R_2 + 3KCN + H_2O}$$
$$\mathrm{\rightarrow R_1COCH_2CH(CN)R_2 + 2KBr + KOCN + HCN}$$

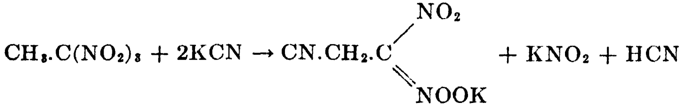
Tetrachloroquinone reacts with potassium cyanide in 85% aqueous methanol solution to form the potassium salt of *cyanoanilic acid, i.e.*, 3,6-dihydroxy-2:5-dicyanoquinone[61]:



Cyanoanilic acid is a strong acid. The nitrile groups in this compound are hydrolyzed to the carboxylic group with great difficulty. The compound is strongly fluorescent.

Dicyanodichlorohydroquinone has been prepared through the action of potassium cyanide on tetrachloroquinone in acetone solution[62].

Potassium cyanide reacts with trinitroethane to form the potassium salt of a nitrated cyanoethane:



$$CH_3.C(NO_2)_3 + 2KCN \rightarrow CN.CH_2.C\begin{matrix}NO_2\\NOOK\end{matrix} + KNO_2 + HCN$$

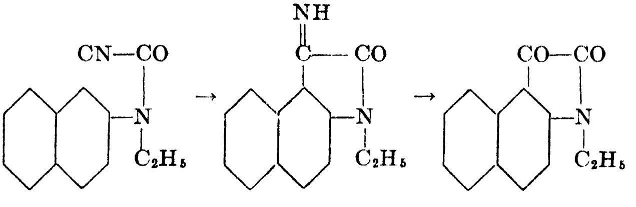
On acidification, the compound is converted to *dinitropropionitrile*. By careful oxidation of the compound with hydrogen peroxide, cyanoacetic acid forms[63]. Potassium cyanide adds to phenylnitroethylene to form a similar compound[64].

The reaction between potassium cyanide and *bromopicrin* appears to proceed in a complicated manner[65], one product of the reaction being potassium tetranitroethane, $KC(NO_2)_2.C(NO_2)_2K$, a compound which explodes by impact or when heated to 270–275°. Basset[66] claimed to have prepared chloronitromalonitrile, $ClC(NO_2)(CN)_2$, from chloropicrin and potassium cyanide, but this claim remains to be substantiated.

Phosgene reacts with hydrocyanic acid in the presence of N-substituted aromatic amines to form *cyanoformamines*. Thus, with β-naphthylethylamine, ethyl-β-naphthylcyanoformamine is formed:

$$2\beta\text{-}C_{10}H_7NH.C_2H_5 + Cl_2CO + HCN$$
$$\rightarrow \beta\text{-}C_{10}H_7.N(C_2H_5).CO.CN + \beta\text{-}C_{10}H_7NHC_2H_5.HCl$$

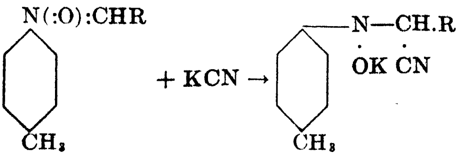
In the presence of aluminum chloride these compounds form N-substituted isatins[67]:



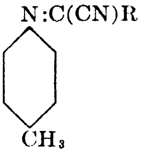
Dichloroethyl sulfide reacts with potassium cyanide in alcoholic solution to form ethylenebiscyanoethyl disulfide in rather poor yield[68]:

$$2(ClCH_2CH_2)_2S + \xrightarrow{KCN} CNCH_2CH_2S\ CH_2CH_2.S.CH_2CH_2CN$$

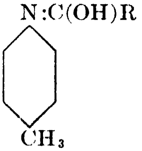
p-Tolyladonitrones react with potassium cyanide to form an addition compound



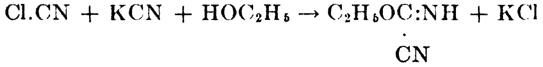
which is not stable in concentrated solution and changes to:



Potassium hydroxide reacts with this to form[69]:

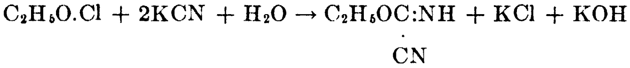


Potassium cyanide reacts with cyanogen chloride in alcoholic solution to form *cyanoformimino ethyl ether:*



$$\mathrm{Cl.CN + KCN + HOC_2H_5 \rightarrow C_2H_5O\underset{\cdot\,CN}{C}{:}NH + KCl}$$

A number of other products are formed simultaneously[70]. The same product is obtained through the interaction of ethyl hypochlorite with potassium cyanide[70]:



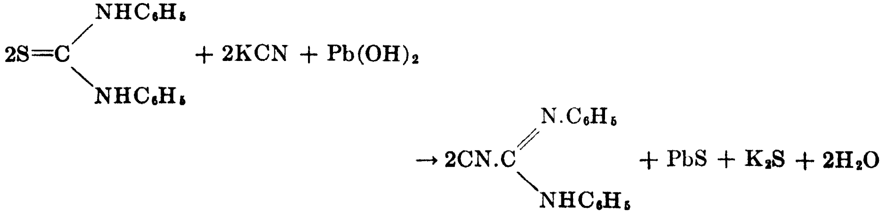
$$\mathrm{C_2H_5O.Cl + 2KCN + H_2O \rightarrow C_2H_5O\underset{\cdot\,CN}{C}{:}NH + KCl + KOH}$$

Chlorine reacts with an aqueous alcoholic solution of potassium cyanide to form diethyl chlorocarbimide[71]:

$$\mathrm{4C_2H_5OH + 2KCN + 4Cl_2 \rightarrow 2(C_2H_5O)_2C{=}NCl + 2KCl + 4HCl}$$

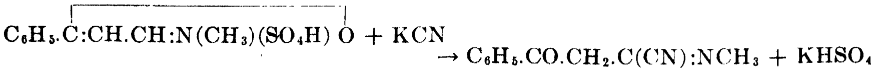
ethyl cyanoformimide and a crystalline chlorinated compound (m.p. 148–149°) being also formed simultaneously[72].

Thiocarbanilide reacts when heated to boiling in an aqueous solution of potassium cyanide containing lead hydroxide in suspension to form *cyanocarbodiphenylimide:*



This compound in turn reacts with ammonium sulfide to form thiocarbaminylocarbodiphenylimide, which is converted with sulfuric acid, to α-isatinanilide and this is hydrolyzed by dilute sulfuric acid to isatin and aniline.

Potassium cyanide reacts with 5-phenylisoxazolemethyl sulfate to form *α-methylimino-γ-keto-γ-phenylbutyronitrile*[73]:



$$C_6H_5.C{:}CH.CH{:}N(CH_3)(SO_4H)\,O + KCN \rightarrow C_6H_5.CO.CH_2.C(CN){:}NCH_3 + KHSO_4$$

Miscellaneous Reactions

In the presence of alcohol, potassium cyanide causes the decomposition of benzil to ethyl benzoate and benzaldehyde, and from this benzoïn results by condensation[74]:

$$C_6H_5.CO.CO.C_6H_5 + HOC_2H_5\ (+\ KCN) \rightarrow C_6H_5CO.OC_2H_5 + C_6H_5CHO$$
$$2C_6H_5.CHO\ (+\ KCN) \rightarrow C_6H_5CH(OH).CO.C_6H_5$$

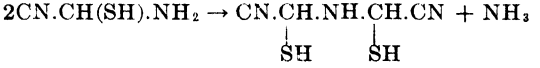
Other compounds containing the group —CO.CO— react in a similar manner. According to Chalanay and Knoevenagel[75], the condensation of benzaldehyde to benzoïn proceeds as follows:

$$C_6H_5CHO + KCN \rightarrow C_6H_5CKO + HCN$$
$$C_6H_5CHO + HCN \rightarrow C_6H_5CH(OH)CN$$
$$C_6H_5CH(OH)CN + C_6H_5CKO \rightarrow C_6H_5CH(OH).COC_6H_5 + KCN$$

When hydrogen sulfide is conducted into a saturated solution of potassium cyanide, a compound of the formula $C_4H_5N_3S_2$ precipitates out. Wallach[76], who first prepared the compound, termed it *chrysean*. Hellsing[77], obtained it by the interaction of potassium cyanide and thioformamid, and assumed that an intermediate compound is first formed as follows:

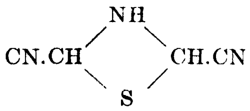
$$HCS.NH_2 + HCN \rightarrow CN.CH(SH)NH_2$$

and that chrysean forms by the interaction of two molecules of this with elimination of ammonia:

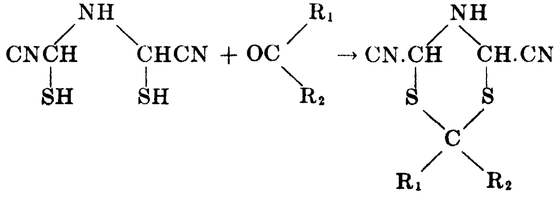


$$2CN.CH(SH).NH_2 \rightarrow CN.\underset{SH}{CH}.NH.\underset{SH}{CH}.CN + NH_3$$

Chrysean is acidic in character; its lead and silver salts are unstable and decompose to the metal sulfide and the compound

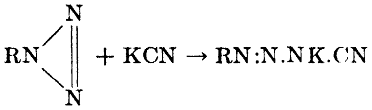


It may be condensed with carbonyl groups as follows[78]:

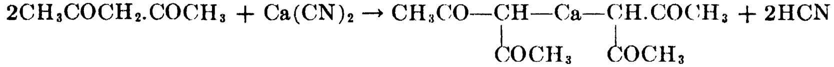


The formyl, benzoyl derivatives have been prepared. The compound has been partially desulfurized to C_2H_5NS, and from this, various derivatives have been prepared, such as cyanobenzylaminothiazole, $C_3HSN(CN).(N:CHC_6H_5)$; acetylaminothiazolecarboxylic amide, $C_3HSN(NH.COCH_3)CONH_2$; and acetylaminothiazole, $C_3H_2SN.NHCOCH_3$[79].

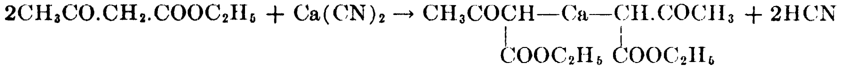
Potassium cyanide reacts with azido compounds, RN_3, to form the potassium salts of cyanotriazine compounds[93]:



Alkaline earth cyanides react with acetylacetone and acetoacetic ester, the metal replacing one active hydrogen in these compounds[94]:



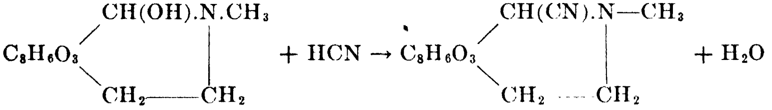
$$2CH_3COCH_2.COCH_3 + Ca(CN)_2 \rightarrow \underset{COCH_3}{CH_3CO—CH}—Ca—\underset{COCH_3}{CH}.COCH_3 + 2HCN$$



$$2CH_3CO.CH_2.COOC_2H_5 + Ca(CN)_2 \rightarrow \underset{COOC_2H_5}{CH_3COCH}—Ca—\underset{COOC_2H_5}{CH}.COCH_3 + 2HCN$$

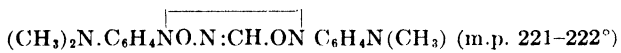
Hydrocyanic acid replaces with a nitrile group the ethoxy group in diphenylethoxyarsine, $(C_6H_5)_2AsOC_2H_5$, and the oxygen in diphenylarsineoxide, $[(C_6H_5)_2As]_2O$, to form diphenylcyanoarsine[95], $(C_6H_5)_2As.CN$.

Certain alkaloids react with hydrocyanic acid, exchanging a hydroxy group with a nitrile group:



Cotarnine reacts similarly[96].

Potassium cyanide reacts with nitrosodimethylaniline on heating in alcoholic solution, forming nitrosodimethylaniline cyanhydrin,

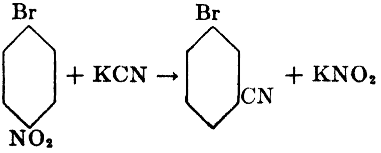


$$(CH_3)_2N.C_6H_4\overline{NO.N:CH.ON}\,C_6H_4N(CH_3) \text{ (m.p. 221–222°)}$$

Nitrosodiethylaniline gives a similar compound[97].

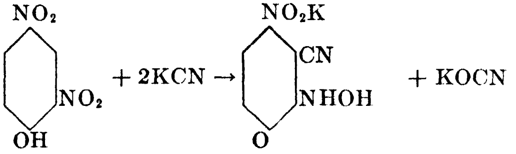
Reaction of Alkali Cyanides with Aromatic Nitro Compounds

Some aromatic mononitro compounds react with potassium cyanide to form a nitrile with the elimination of the nitro group. The CN-group does not, however, replace the nitro group but enters a neighboring position. Thus, *p*-nitrobromobenzene yields *m*-bromobenzonitrile:



By this method have been prepared also *m*-chlorobenzonitrile, *o*-bromobenzonitrile, 1,4-dibromobenzonitrile, 3,5-dibromobenzonitrile from *p*-nitrochlorobenzene, *m*-nitrobromobenzene, 1,4-dibromo-2-nitrobenzene, 1,5-dibromo-4-nitro benzene, respectively. Compounds in which the nitro group is in the *ortho* position with respect to bromine fail to react[80].

Certain dinitro compounds react with potassium cyanide to form *meta purpurates*[81]:



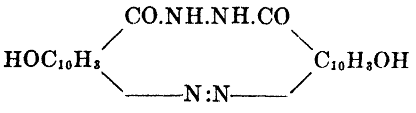
The free acid is not stable and rapidly changes to a resinous mass with liberation of nitrogen.

Mononitrophenols do not give this reaction; of dinitrophenols, only the 2,4- and 2,6-compounds form purpurates. Thus, the reaction proceeds only when at least two nitrogroups are present, and these must be in the *meta*-position with respect to one another; moreover, at least one of the nitro groups should be in the *ortho* position with respect to the hydroxyl group.

2,4-Dinitro-*o*-cresol adds one cyano group, whereas 2,6-dinitro-*p*-cresol forms a dicyano compound[82]. In general, 2,6-dinitrophenols appear to form dicyano compounds if the 3- and 5-positions are not occupied with substituents.

The introduction of an amino group in the molecule of 2,4-dinitrophenol causes a decrease in the tendency to form a purpurate and a considerable portion of dinitronitrile, $H_2N(OK).C_6H.(NO_2)_2CN$, is formed when the amino compound is made to react with potassium cyanide[83]. The introduction of a carboxy group in the molecule of a dinitrophenol does not materially influence the course of the purpurate reaction[84]. The free purpuric acids have been obtained by decomposing the potassium salts with phosphoric acid. The acids are more stable in ether solution than in the isolated form[85].

Naphthylpurpuric acid, $C_{10}H_5(OH)(NO_2)N{:}CH.NO$, has been prepared from dinitronaphthol and potassium cyanide. An indigo-like compound, indophan,

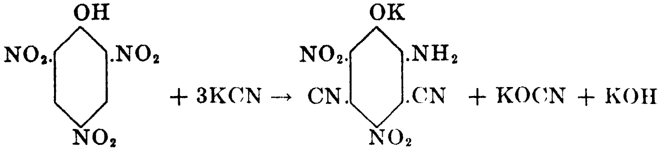


forms simultaneously[86].

Dinitrobenzene and dinitronaphthalene react with potassium cyanide to form colored or tarry products. A crystalline blue compound, $C_{28}H_{19}KN_8O_{10}$, has been isolated from the reaction product of dinitronaphthalene[87].

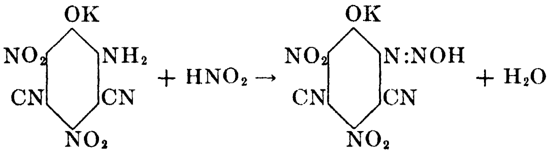
According to de Bruyn[88], potassium cyanide reacts with *meta*-dinitrobenzene in alcoholic solution to form 1-nitro-3-methoxy-4-cyanobenzene; in aqueous solution the reaction product is 1-hydroxy-6-nitrobenzonitrile.

Potassium cyanide reacts with *picric acid* to form a deeply purple-colored compound, which is the potassium salt of *isopurpuric acid*[89]:



The free acid is not capable of existance. The same compound is formed through the interaction of hydrocyanic acid and alkali picrate. This reaction forms the basis of the *picrate test* for hydrocyanic acid.

Hydrogen chloride in acetic acid solution gives with potassium isopurpurate the highly explosive compound potassium dinitrodicyanohydroxydiazobenzol:



The nitrous acid required for the reaction is formed through the decomposition of some of the isopurpuric acid[130].

Cuprous- and silver cyanides do not react with picric acid or picrates. Zinc cyanide reacts slowly with ammonium picrate, forming ammonium isopurpurate; with picric acid, it gives a mixture of zinc- and ammonium isopurpurates[90].

Chrysamic acid reacts with potassium cyanide in the same manner as picric acid, forming the compound[91], $C_{18}H_2KNO_6O_{12}$.

Potassium cyanide reacts in aqueous solution with α-nitroso-β-naphthol at 80 to 90°, forming 1-amino-2-hydroxy-4-cyanonaphthalene[92]:

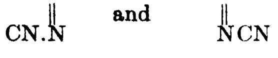
$$C_{10}H_6(OH)NO + KCN + 2H_2O \rightarrow C_{10}H_5(OH)(NH_2).CN + K_2CO_3 + NH_3$$

Reaction of Alkali Cyanides with Diazo Compounds

Hantzsch and Schultze[93] showed that diazonium compounds react with alkali cyanides at ordinary temperature to form diazo cyanides:

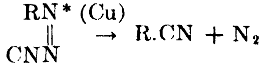
$$RN{:}NCl + KCN \rightarrow R.N{:}NCN + KCl$$

The compounds are normal nitriles and exist in two forms, the *cis* and the *trans*-isomers:



$$\begin{array}{c} RN \\ \| \\ CN.N \end{array} \quad \text{and} \quad \begin{array}{l} RN \\ \| \\ NCN \end{array}$$

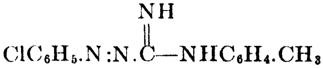
The *cis*-isomer forms at temperatures below zero, and is the unstable form; it gradually changes to the *trans*-isomer, the more rapidly, the higher the temperature. The change takes place more readily in solution, especially in alcoholic solution. The *cis*-isomer decomposes readily to nitrogen and an organic nitrile when heated in solution in the presence of copper powder:



$$\begin{array}{l} \mathrm{RN^{*}\ (Cu)} \\ \quad \| \qquad \rightarrow \mathrm{R.CN} + \mathrm{N_2} \\ \mathrm{CNN} \end{array}$$

The *trans*-isomer does not undergo this change. Diazo colors may be obtained from the *cis*-isomer, but not from the *trans*-isomer.

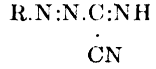
The CN-group in these compounds shows the characteristic reactions of this group to an enhanced degree. It readily forms iminoethers, and readily yields amides and acids by hydrolysis. The amides form by simple boiling with water; acids are obtained by alkaline hydrolysis. The acids and iminoethers are quite unstable; diazocarboxylic acids decomposing vigorously when dry. Hantzsch and Schultze[99] prepared amidines, such as chlorodiazobenzyltolylguanidine



$$\mathrm{ClC_6H_5.N{:}N.\overset{\overset{\displaystyle NH}{\|}}{C}{-}NHC_6H_4.CH_3}$$

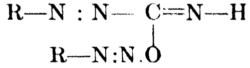
from chlorodiazobenzene cyanide and *p*-toluidine in alcoholic solution, in the presence of a little alkali.

Diazocyanides combine with one molecule of hydrocyanic acid. Hantzsch and Schultze considered the resulting compounds to be diazocarbimine cyanides



$$\mathrm{R.N{:}N.\underset{\displaystyle \overset{\cdot}{C}N}{C}{:}NH}$$

When the reaction between diazo compounds and alkali cyanides is carried out in the presence of some free alkali, a molecular compound of the diazo cyanide with free diazonium hydroxide forms, which is probably α diazoxydiazocarbamide[100],

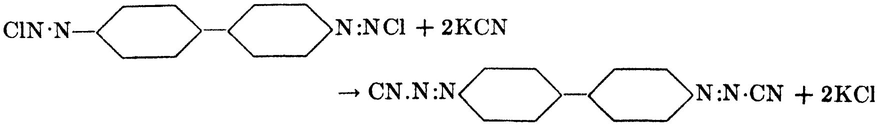


$$\begin{array}{l} \mathrm{R{-}N : N{-}\ C{=}N{-}H} \\ \qquad\qquad\quad | \\ \quad \mathrm{R{-}N{:}N.O} \end{array}$$

This reaction takes place only with the *cis* isomers. These compounds are strongly acidic, the hydrogen in the molecule being replaceable with metals.

Hantzsch and Schultze[101], Hantzsch[102] and Hantzsch and Danziger[103] prepared benzenediazo cyanide, *p*-nitrobenzenediazo cyanide, *p*-chlorobenzenediazo cyanide, as well as other halobenzenediazo cyanides, anisolediazo cyanide, pseudocumoldiazo cyanide and naphthalenediazo cyanide.

Le Fèvre and Vione[104] prepared diphenyl-4,4′-bisdiazo cyanide (m.p. 97° with dec.) from 4,4′-bisdiazodiphenyl chloride and potassium cyanide;



Acetoneazo cyanide, $CH_3CO.CH_2N{:}N.CN$, has been prepared through the interaction of diazoacetone chloride and potassium cyanide and isolated as the semicarbazone[105].

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* Le Fèvre and Vione have obtained independent proof of the correctness of this structure assigned to the unstable isomer. (*J. Chem. Soc.*, **1938**, 431).

Preparation of Nitriles from Diazonium Compounds. *Cis*-diazo cyanides form double compounds with cuprous and mercuric cyanides. This fact undoubtedly plays a part in *Sandmeyer's method*[106] for the preparation of nitriles from diazonium compounds, which comprises heating a solution of the diazonium compound and cuprous potassium cyanide:

$$RN_2Cl + KCN.CuCN \rightarrow RCN + N_2 + KCl + CuCN$$

With benzenediazonium chloride, a 65% yield of benzonitrile may be obtained.

Nitriles may also be obtained from diazonium compounds by heating a solution of the diazonium compound and alkali cyanide in the presence of finely divided metallic copper[107] (Gattermann's method). With benzenediazonium sulfate, a 60% yield of benzonitrile may be obtained. It should be remarked that Gattermann's reaction is favored only when ionization is possible. The reaction may well be one involving a diazonium compound[108].

Example: Preparation of p-Tolyl Cyanide from p-Toluidine. Fifty grams of copper sulfate are dissolved in 200 cc of water heated on a water bath to 60-70° and a solution of 55 grams of potassium cyanide in 100 cc of water is introduced gradually. To this solution is added, in the course of 10 minutes, the diazotoluene chloride, prepared as follows: 20 grams of *p*-toluidine are dissolved by the application of heat in a mixture of 50 grams of concentrated hydrochloric acid and 150 cc of water. The solution is rapidly chilled in ice water, thus causing the separation of the toluidine hydrochloride in fine crystals. A solution of 16 grams of sodium nitrite in 80 cc of water is then added to the amine hydrochloride suspension under good cooling until a permanent reaction of nitrous acid upon the starch-potassium iodide paper is obtained. The reaction mixture is finally heated on the water bath for about a quarter of an hour and the nitrile formed is distilled with steam. The crude nitrile is purified by fractional distillation. Since hydrocyanic acid is evolved during the operation, the reaction should be carried out under a hood with *efficient draft.*

2-Nitro-4-tolunitrile has been obtained by this reaction in 80% yield[109]. *o-Nitrobenzonitrile* has been prepared from *o*-nitraniline in approximately 70% yield[110]. *p-Chloro-m-nitro-*, *p-chlor-o-nitro-* and *m-chloro-p-nitrobenzonitriles* have also been made by Sandmeyer's method[111].

α-Cyanonaphthalene has been prepared from α-naphthyldiazonium chloride by reaction with the double cyanide of nickel and potassium with a 58-66% yield[112]. *β-Cyanonaphthalene* has also been prepared by the Sandmeyer reaction. Varying yields have been reported by various authors[113].

Naphthenesulfonic nitriles have been prepared from the corresponding amino sulfonates by Sandmeyer's reaction. The yields were as follows[114]:

	Yield, %
1-cyano-2-sulfo-	64
1-Cyano-3-sulfo-	100
1-Cyano-4-sulfo-	81
1-Cyano-5-sulfo-	65
1-Cyano-6-sulfo-	88
1-Cyano-7-sulfo-	ca. 50
1-Cyano-8-sulfo-	77
2-Cyano-6-sulfo-	65
2-Cyano-7-sulfo-	80

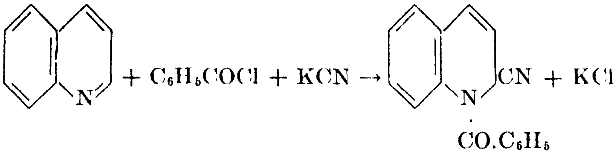
2-Amino-3-sulfonaphthalene yields 2:3 naphthalimide, m.p. 273°.

The Sandmeyer reaction is applicable to pyridine and its derivatives. Thus, Räth and co-workers[115] have prepared the following from the corresponding amines:

	Yield, %
2-Me-5-cyanopyridine	40
2-Cl-5-cyanopyridine	40
2,3-Dichloro-5-cyanopyridine	30
2-Cl-3-Br-5-cyanopyridine	30
2-Cl-3-I-5-Cyanopyridine	45
2-Hydroxy-3-cyano-5-I-pyridine	07
2,5-Dichloro-3-cyanopyridine	
3-Cyanopyridine	

Reissert Compounds

The fact that the product of the reaction of hydrocyanic acid and benzoyl chloride in the presence of quinoline is the so-called Reissert compound, or 1-benzoyl-2-cyano-1,2-dihydroquinoline (1-benzoyl-1,2-dihydroquinaldonitrile), has been mentioned. The compound forms readily through the interaction of potassium cyanide with benzoyl chloride and quinoline[34]



The preparation may be carried out as follows:

To a solution of 135 grams of potassium cyanide in 850 cc of water are added 90 grams of quinoline; the liquid is agitated while 203 grams of benzoyl chloride are introduced gradually. The whole of the benzoyl chloride should be introduced within eight to ten minutes. Agitation is continued for ten more minutes, and the yellow precipitate is separated from the deeply colored solution. Two to three hundred cubic centimeters of 10% hydrochloric acid are added; the solid is filtered, washed and crystallized from ether. The yield of crude product (m.p. 153–154°) is about 170 grams, or approximately 94.5% of the theoretical[116].

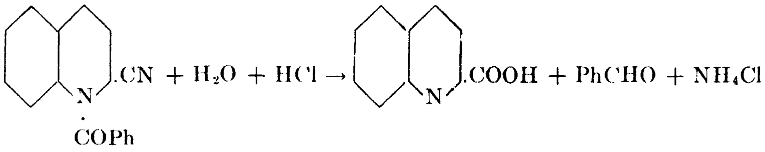
Acetyl chloride and other aliphatic acid chlorides do not form Reissert compounds by this method but give acyl cyanides. A large proportion of acyl cyanide also forms in the reaction with benzoyl chloride. No reaction takes place when acetyl cyanide, phenyl cyanide, ether, dioxane, acetone or chloroform are substituted for water in the original Reissert method.

Grosheintz and Fischer[117] prepared Reissert compounds from aliphatic as well as aromatic acid chlorides by the following method:

Two to three cubic centimeters of hydrocyanic acid were dissolved in 14 grams of quinoline, the solution was cooled to $-5°$ and 0.05 mole of acid chloride dissolved in 10–20 cc of anhydrous benzene was added gradually in the course of 10 minutes. The mixture was allowed to stand 16 hours; one to two hundred cubic centimeters of ether were then added, and the solution was washed successively with water, 5-*N* sulfuric acid, a saturated solution of sodium bicarbonate and finally with water again. The following compounds were prepared

	M.P., °C	Yield %
1-Acetyl-1,2-dihydroquinaldonitrile	96–97	74
1-Propionyl-1,2-dihydroquinaldonitrile	49–50	10
1-Butyryl-1,2-dihydroquinaldonitrile	97.5	64
1-Isobutyryl-1,2-dihydroquinaldonitrile	192–199.5	28
1-Isovaleryl-1,2-dihydroquinaldonitrile	90–90.5	64
1-(2-Methoxybenzoyl)-1,2-dihydroquinaldonitrile	164–164.5	66
1-(4-Methoxybenzoyl)-1,2-dihydroquinaldonitrile	120.5–121.5	88
1-(*o*-chlorobenzoyl)-1,2-dihydroquinaldonitrile	165–168	80
1-(*m*-Chlorobenzoyl)-1,2-dihydroquinaldonitrile	116–119	28
1-(*p*-Chlorobenzoyl)-1,2-dihydroquinaldonitrile	140–143	77
1-Cinnamoyl-1,2-dihydroquinaldonitrile	154–155	91
1-Benzoyl-1,2-dihydroquinaldonitrile	154–155	96

Reissert's compounds decompose by the action of concentrated hydrochloric acid or other strong mineral acids to quinaldic acid and an aldehyde[118].



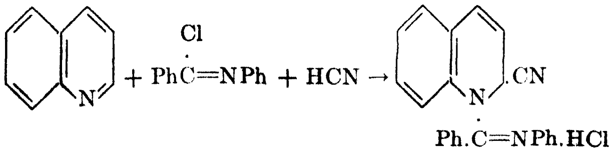
This reaction offers a method for the preparation of aldehydes from acid chlorides. Sugasawa and Tsuda[118] prepared the following:

	Yield, %
1-Anisoyl-1,2-dihydroquinaldonitrile	50.6
1-Veratroyl-1,2-dihydroquinaldonitrile	36.2
1-Trimethylglycolyl-1,2-dihydroquinaldonitrile	slight
1-Cinnamoyl-1,2-dihydroquinaldonitrile	34

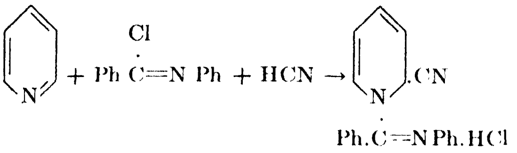
From these the corresponding aldehydes were obtained in yields varying between 34 and 57%.

The catalytic reduction of Reissert's compound with Basler nickel at 90° under 70 atm. for 24 hours leads to the formation of 1-benzoylaminomethyltetrahydroisoquinoline[119].

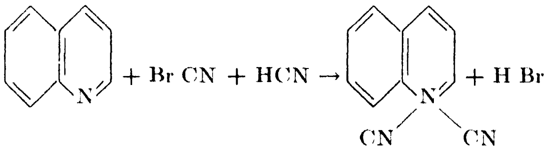
Benzanilimido chloride reacts with quinoline in the presence of hydrocyanic acid, probably forming 1,2-dihydroquinaldonitrilebenzylidineaniline hydrochloride[120]:



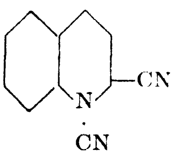
A similar reaction also takes place with pyridine:



Cyanogen bromide reacts with quinoline in the presence of hydrocyanic acid to form a dicyanide[121]:

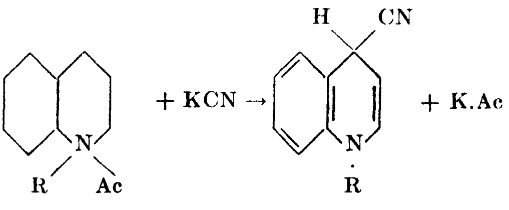


In alcoholic ammonia, this compound is converted to its isomer 1-cyano-1,2-dihydroquinaldonitrile:



The reaction may, therefore, be considered similar to that giving rise to Reissert compounds. The reaction also takes place with *p*-toluquinoline and β-naphthoquinoline, but *not* with *o*-toluquinoline, α-naphthoquinoline, pyridine and acridine. Cyanogen chloride reacts in a similar manner. Cyanogen iodide also gives an addition compound, C_9H_7.N.ICN, with quinoline, but this differs from the corresponding chloro or bromo compound, in that it does not form a dicyanide with HCN or with NaCN[122].

Quaternary ammonium compounds of quinoline react with potassium cyanide in cold aqueous solution to give a quaternary cyanide which changes to a 4-cyanoquinoline:



These compounds may be oxidized with iodine to the cyano quaternary ammonium compounds and these, by pyrolysis, form cyano quinoline[123]. Quaternary salts of acridine react in a similar manner, forming N-methyl-9-cyanoacridane[124].

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Chapter 8

Reduction of Nitriles

The partial hydrogenation of nitriles leads to the formation of amines:

$$RCN + 2\,H_2 \rightarrow RCH_2NH_2$$

Further hydrogenation produces a hydrocarbon and ammonia:

$$RCH_2NH_2 + H_2 \rightarrow RCH_3 + NH_3$$

Reduction may be accomplished chemically with nascent hydrogen, catalytically, or, in special cases, electrolytically. Catalytic reduction may be carried out under widely varying conditions of temperature and pressure, in the gas phase, or in the liquid phase. Nitriles vary in the ease with which they are hydrogenated. Thus for example, aliphatic nitriles are reduced more readily than aromatic nitriles in which the CN-group is attached directly to the aromatic nucleus. Reduction seldom proceeds in the simple manner indicated above, however, as will be seen subsequently.

Reduction of Hydrocyanic Acid

Reduction by Use of Platinum as a Catalyst. It may be considered an established fact that hydrocyanic acid may be hydrogenated to methylamine by the use of platinum catalyst.

Dubus[1] reduced hydrocyanic acid in the vapor phase with hydrogen to methylamine in the presence of platinum black, in the temperature range 100°–110°. He observed that the catalyst lost its activity quite rapidly. Linnemann[2] reduced hydrocyanic acid vapors at 300°, in the presence of platinum sponge. Reduction proceeded readily and the contact mass was apparently not attacked, but it soon lost much of its activity due to sintering. Denham[3] obtained methylamine by reducing hydrocyanic acid in solution in the presence of platinized platinum. Riedel[4] and independently Sieverts and Peters[5] carried out the reduction in the presence of colloidal platinum.

Barratt and Titley[6], using platinized asbestos as a catalyst, found that the favorable temperature range was 120° to 250°. In addition to methylamine, di- and trimethylamines and ammonia were obtained:

The formation of di- and trimethylamines and ammonia may be explained in various ways: The first stage of the reaction may well be the formation of formaldimine, $H_2C{:}NH$, which, reacting with the methylamine already formed would give aminomethylmethyamine $NH_2CH_2.NH.CH_3$; hydrogenation of this compound would lead to the formation of dimethylamine and ammonia. The formation of trimethylamine may be similarly explained by assuming the formation of aminomethyldimethylamine from formaldimine and dimethylamine and its subsequent reduction. Di- and trimethylamines may also result from the thermal condensation of mono- and di-ethylamines, ammonia being produced simultaneously:

$$2CH_3NH_2 \rightarrow (CH_3)_2NH + NH_3$$
$$(CH_3)_2NH + CH_3NH_2 \rightarrow (CH_3)_3N + NH_3$$

Ammonia may, of course, also result from the reduction of methylamine and di- and trimethylamines.

The partial pressure of hydrocyanic acid in the reaction mixture is found to have a marked influence on the proportion of the various bases formed, a low partial pressure of hydrocyanic acid in the original mixture favoring the formation of monomethylamine. When the ratio of hydrocyanic acid to hydrogen was maintained at 1:15, an 80% yield of bases was obtained, of which 75% was monomethylamine. Yields of monomethylamine up to 90% have been obtained with platinized asbestos by using a large excess of hydrogen and maintaining the space velocity within a well-defined range[7].

Reduction by Use of Base-Metal Catalysts. Hydrocyanic acid may be reduced in the presence of base-metal catalysts, especially finely divided nickel, but the products are largely ammonia and methane with comparatively small quantities of methylamine. Sabatier and Senderens[8] reduced hydrocyanic acid vapors in the presence of a nickel catalyst at 250°, and identified ammonia, mono-, di- and trimethylamines in the products of reduction.

Dreyfuss[9] reduced gaseous hydrocyanic acid in the presence of a large excess of hydrogen in the temperature range 200–350°, using copper, zinc and nickel cyanide catalysts deposited on pumice. He claimed to have obtained methylamine with small amounts of di- and trimethylamines and ammonia. Metallic copper, zinc, cobalt, tin or silver catalysts gave similar results.

Dreyfuss also reduced a 30% solution of potassium cyanide in an autoclave at 175–180° under a hydrogen pressure of 15 atmospheres and in the presence of nickel cyanide deposited on pumice. Reduction proceeded well in the presence of the cyanides of copper, zinc, iron, cobalt, tin or silver.

Barratt and Titley[6] reduced hydrocyanic acid in the presence of an iron catalyst at 200°. They claimed to have obtained a 45% yield of monomethylamine. Recent work indicates that partial yields of methylamine may be obtained with nickel catalysts[7].

A method of hydrogenation of hydrocyanic acid in the liquid phase in the presence of base metal catalysts is described in *German patent* 496,980. An electrolyte is used in connection with this catalyst. As an example, an aqueous solution of potassium cyanide and ferrous sulfate was hydrogenated in the presence of a nickel catalyst. Yields as high as 90% of methylamine are claimed.

Pedolin[11] studied the vapor phase hydrogenation of hydrocyanic acid in the presence of base metal catalysts, the results indicating that both the hydrocyanic acid-hydrogen ratio and the temperature are important factors determining the proportion of the various bases formed. Best yields of monomethylamine were obtained when the ratio of hydrocyanic acid and hydrogen was maintained at 1:12. The optimum temperature was in the neighborhood of 240°.

Pedolin[11] in common with other investigators, was led to believe that a relatively high proportion of monomethylamine formed in the reduction of hydrocyanic acid with base-metal catalysts. There is reason to believe, however, that the methods of analysis employed by early workers was not entirely reliable and that the proportion of methylamine formed was probably lower than was believed to be the case.

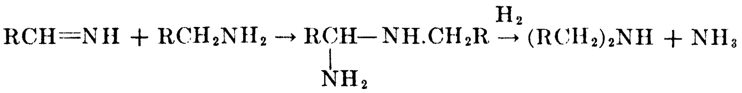
Reduction with Nascent Hydrogen. Mendius[12] reduced hydrocyanic acid in aqueous solution with nascent hydrogen, generated by the interaction of zinc and dilute sulfuric acid. He also carried out the reduction of hydrocyanic acid in alcoholic solution by the use of hydrogen chloride in solution and metallic zinc. Approximately one quarter of the hydrocyanic acid used was recovered in the form of bases.

Brunner and Rapin[13] reduced hydrocyanic acid in neutral solution with a magnesium-copper couple, and with Devarda's alloy (50% Cu, 45% Al, 5% Zn). The resulting products were formaldehyde and ammonia.

Reduction of Nitriles

As a rule, primary and secondary amines form simultaneously when nitriles are catalytically reduced in the presence of nickel or other catalysts. The explanation of this fact is that aldimines* are formed as the first stage of the reduction. As reduction proceeds and the primary amine accumulates in solution, the aldimine reacts with it to form an amino-diamine, which on further reduction yields the secondary amine:

$$RCN \rightarrow RCH{:}NH \rightarrow RCH_2.NH_2$$



$$RCH{=}NH + RCH_2NH_2 \rightarrow \underset{\displaystyle NH_2}{RCH}{-}NH.CH_2R \xrightarrow{H_2} (RCH_2)_2NH + NH_3$$

In the presence of water the reaction may follow another course. The aldimine may be hydrolyzed to the corresponding aldehyde, which then reacting with any primary base already formed gives the corresponding aldimine; this on further reduction yields the secondary base[14].

$$RCH{=}NH + H_2O \rightarrow RCHO + NH_3$$

$$RCHO + H_2N.CH_2R \rightarrow H_2O + RCH{:}NCH_2R \xrightarrow{H_2} (RCH_2)_2NH$$

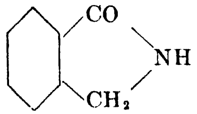
The formation of the primary base may be facilitated in various ways. Thus, if the reduction is carried out in acetic anhydride, the primary base is acetylated as fast as it is formed and a nearly quantitative yield of the acetylated base may be obtained. If the reduction is carried out in aqueous solution, the presence of phenylhydrazine favors the formation of the primary base by eliminating the aldehyde resulting from the hydrolysis of the aldimine. The presence of a large quantity of ammonia also favors the formation of the primary base, probably by repressing the reaction between the primary amine and the aldimine. Schwoegler

* Under reduced pressure the hydrogenation proceeds only to the aldimine stage, [Escourrou, R., *Bull. Soc. Chim.*, (4) **45**, 735 (1929); Grignard, V. and Escourrou, R.. *Compt. rend.*, **180**, 1883 (1925)].

and Adkins[73] were the first to make use of this method and prepared *n*-pentyl- and *n*-heptylamine from the corresponding nitriles in excellent yield. Methylated amines are formed when the reduction is carried out in liquid methylamine[98].

Reduction of Nitriles Containing No Other Reactive Functional Groups. Rupe and co-workers carried out the reduction of a number of nitriles at room temperature and atmospheric pressure, using nickel as a catalyst. The quantities of primary and secondary amines formed from various nitriles were as follows[15]:

	Primary Amines %	*Secondary Amines* %
α-Naphthonitrile	3.3	40
β-Naphthonitrile	....	15
1,5-Bromonaphthonitrile	46.5	7.1
2,5-Bromonaphthonitrile	62.5	2.5
1-Cyannonaphthalene-4-sulfonic acid	good yield	none
o-Hydroxybenzonitrile	none	
o-Tolunitrile	48	17
m-Tolunitrile	52	19
p-Tolunitrile	50	17
o-Bromobenzonitrile	35	23
m-Bromobenzonitrile	47	25
p-Bromobenzonitrile	40	30
o-Cyanobenzoic methyl ester[1]		
m-Cyanobenzoic methyl ester	28	40
p-Cyanobenzoic methyl ester	16	47

[1] Gave phthalimidine  in 90% yield.

Propionitrile gave no appreciable amount of a base; *n*-butyl cyanide gave sec. di-*n*-amylamine[16]. Stearonitrile and other higher aliphatic nitriles have been reduced to primary and secondary amines in presence of nickel catalyst at 220°[78]. α-Naphthonitrile formed dinaphthylamine in 71% yield when reduced in aqueous alcoholic acetic acid solution at 75° under 75 atm. hydrogen pressure[17].

At ordinary temperature and under atmospheric pressure, the reduction of diphenylacetonitrile in the presence of nickel catalyst takes place slowly and the main product is the primary base, unsymmetrical diphenylethylamine. Triphenylacetonitrile is also reduced slowly, and the only product is the primary base.

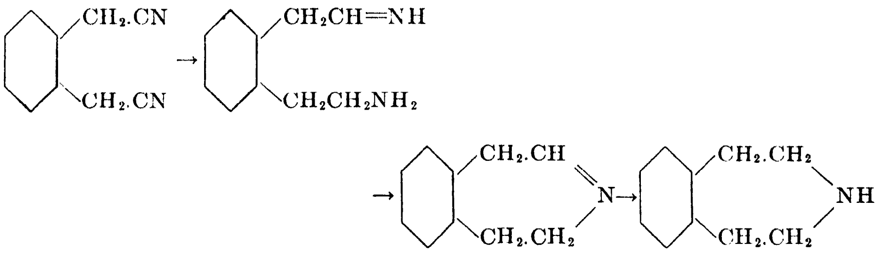
β-Cyanopyridine, hydrogenated in the presence of Raney nickel, gave β-pyridyl methylamine in 42% yield, and di-(β-pyridylmethyl)amine in 48% yield[74].

Vapors of benzonitrile are reduced with hydrogen at 200° in the presence of nickel catalyst to dibenzylamine, some ammonia and toluene forming simultaneously[18]. The reduction of the nitrile under pressure in the presence of a nickel catalyst results in the formation of benzylamine and benzylidine benzylamine, $C_6H_5CH{=}N.CH_2C_6H_5$. On further reduction, this is converted to dibenzylamine[19]. Benzylamine-4-carboxylic acid has been obtained in 80% yield through the reduction of *4-carboxybenzonitrile* in aqueous ammonia in the presence of Raney nickel.[90]

Benzyl cyanide, reduced in ethanol solution in the presence of 2% sodium hydroxide by the use of Raney nickel at room temperature, has been converted to β-phenylethylamine in 92% yield[91]. The reduction of benzyl cyanide in ethanol solution by use of copper chromite, at 200° under 160 atm. resulted in the formation of β-phenyltriethylamine and ethyl-bis (β-phenylethyl) amine. If the reduction is carried out in alcoholic acetic acid, β-phenylethylethylamine and bis-(β-phenylethyl)amine result[92].

Trimethylene dinitrile, $CN.CH_2.CH_2.CH_2CN$, in solution in a mixture of alcohol and ethyl acetate reduced in the presence of a nickel catalyst gives piperidine in good yield; 2-methylpentane-1,3-dinitrile gives β-ethyl-γ-methylpiperidine under the same conditions[79].

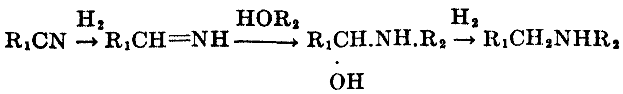
Ruggli and co-workers[20] prepared primary phenylenediethylamines from phenylene diacetonitriles by catalytic hydrogenation with nickel at 90–100° under 75 atm. pressure in the presence of a large amount of ammonia. The primary diamines were obtained in 57% yield from *m*- and *p*-phenylene diacetonitriles. The ortho isomer gives a cyclic imine, *sym.* homotetrahydroisoquinoline:



The *m*- and *p*-isomers, reduced in methanol solution in the presence of ammonia at 90–95°, under 80–90 atm. pressure, give the primary amines $C_6H_4(C_2CH_2HNH_2)_2$, in 78.5% and 75% yield respectively.

Braun and co-workers[21,22] investigated the catalytic reduction of nitriles in solution under a pressure of 20 atmospheres. With the exception of naphthonitrile, which could only be reduced between 180 and 190°, all nitriles investigated gave high yields of amines in the temperature range of 110–130°. The total yields ranged from 80 to 95% of theory. Both primary and secondary amines were obtained in every case; the amount of tertiary amines formed was negligible.

> In general, variations in pressure and temperature exerted a negligible influence on the nature of the products; on the other hand, the character of the solvent used and the concentration of the nitrile were found to be important factors. Alcohols, particularly those with active hydroxyl groups, took part in the reaction to form mixed bases:

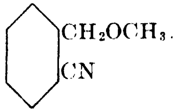
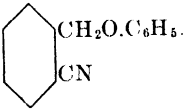
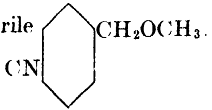
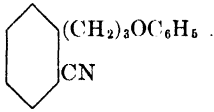


$$R_1CN \xrightarrow{H_2} R_1CH{=}NH \xrightarrow{HOR_2} R_1\underset{OH}{CH}.NH.R_2 \xrightarrow{H_2} R_1CH_2NHR_2$$

The proportions of primary and secondary amines obtained by Braun, Blessing and Zobel[21] are presented in the table which follows:

	% Bases	
Nitrile	*Primary*	*Secondary*
Capronitrile, $C_7H_{15}CN$	15	18
Phenoxypropionitrile, $C_6H_5OCH_2CH_2CN$	29	47
Benzonitrile[18], C_6H_5CN	41	35
α-Naphthonitrile, $\alpha.C_{10}H_7CN$	70	21
β-Naphthonitrile, $\beta.C_{10}H_7CN$	66	17
Benzyl cyanide, $C_6H_5.CH_2CN$	35	27
β-Phenylpropionitrile, $C_6H_5CH_2CH_2.CN$	21	43
o-Tolunitrile, o-$CH_3C_6H_4CN$	61	17
m-Tolunitrile, m-$CH_3C_6H_4CN$	54	32
p-Tolunitrile[18], p-$CH_3C_6H_4CN$	41	32

The yields of mono- and diamines from substituted aromatic nitriles reduced in tetra- or decahydronapthalene were in the proportions given below:

Nitrile	*Temp.,* °*C*	*Proportion of Mono- and Diamine*
ω-Methoxy-o-tolunitrile 	100	2:1
ω-Phenoxy-o-tolunitrile 	10	4:1
ω-Methoxy-p-tolunitrile 		
o-(γ-Phenoxypropyl)-benzonitrile 	115	1:1

Rupe and Glenz[24], using nickel as a catalyst, prepared dihexylamine, diphenylethylamine and diphenylpropylamine from amyl cyanide, benzyl cyanide and phenylethyl cyanide, respectively.

Rupe and Hodel[25], also using nickel as a catalyst, prepared diisoamylamine from isobutyl cyanide (yield about 77%).

Both primary and secondary amines are formed when benzo- and tolunitrile are reduced in alcoholic acetic acid solution, in the presence of platinum catalyst. The results obtained by Carothers and Jones[26] are shown in the following table:

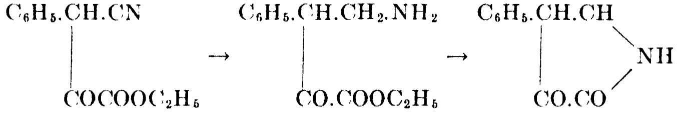
	Solvent	*%* *Primary Amine*	*%* *Secondary Amine*
Benzonitrile	Alcohol	21	79
	Acetic Acid	62	38
p-Tolunitrile	Alcohol	33	67
	Acetic Acid	4	84

When the reduction is carried out in acetic anhydride, the acetyl derivative of the primary amine alone is formed.

Paal and Gerum[27] reduced benzonitrile in aqueous-alcoholic solution in the presence of colloidal palladium and obtained mono- and dibenzylamines.

β-Cyanomethylnaphthalene may be reduced at room temperature under one atmosphere pressure in a mixture of sulfuric and acetic acids in the presence of palladium-carbon as a catalyst to form β-(naphthyl-2)-ethylamine, b.p. 168–169° under 19 mm. In the same manner, β-(naphthyl-1)-ethylamine (b.p. 178–181° under 20 mm) may be obtained from α-cyanomethylnaphthalene[28].

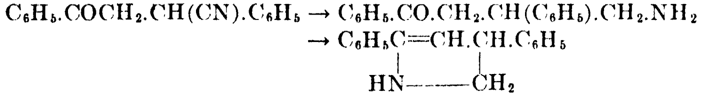
Reduction of Nitriles Containing Carbonyl Groups. In the presence of nickel catalyst and at atmospheric pressure, phenylcyanopyruvic ethyl ester is reduced at 50–55° quantitatively to 4-phenyl-2,3-diketopyrrolidine[29]:



Benzoylcyanoacetic ethyl ester is reduced at 68–73° to α-methylbenzoylacetic ethyl ester[29]:

$$
\begin{aligned}
&C_6H_5.CO.CH(CN).COOC_2H_5 \rightarrow C_6H_5.CO.CH.(CH{:}NH).COOC_2H_5\\
&\rightarrow C_6H_5COCH(CHO).COOC_2H_5 \rightarrow C_6H_5.CO.CH(CHOH)COOC_2H_5\\
&\rightarrow C_6H_5.CO.C({:}CH_2).COOC_2H_5 \rightarrow C_6H_5CO.CH(CH_3).COOC_2H_5
\end{aligned}
$$

α-Phenyl-β-benzoylpropionitrile yields a primary base as the main product, which immediately forms 2,4-diphenylpyrroline, m.p. 40°, in 95% yield:



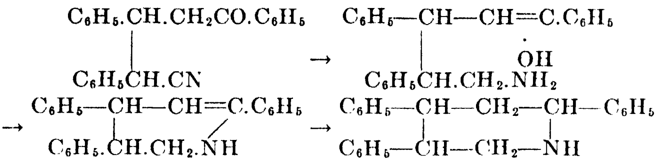
$$
\begin{aligned}
&C_6H_5.COCH_2.CH(CN).C_6H_5 \rightarrow C_6H_5.CO.CH_2.CH(C_6H_5).CH_2.NH_2\\
&\rightarrow \begin{array}{l} C_6H_5C{=}CH.CH.C_6H_5 \\ \quad | \qquad\quad | \\ \ HN\text{———}CH_2 \end{array}
\end{aligned}
$$

2-Phenyl-4-*p*-anysylpyrroline, m.p. 27°, and 4-phenyl-2-*p*-anisylpyrroline, m.p. 74.5° have been prepared similarly from β-benzoyl-α-*p*-anisylpropionitrile and β-*p*-anisoyl-α-phenylpropionitrile respectively[31].

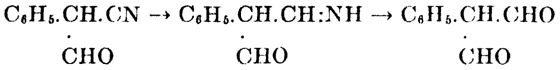
The reduction of cyanodesoxybenzoin proceeds differently; an aldimine and an aldehyde are the products formed[30]:

$$
\begin{aligned}
&C_6H_5.CO.CH(CN).C_6H_5 \rightarrow C_6H_5.CO.CH(CH{:}NH).C_6H_5\\
&\rightarrow C_6H_5CO.CH(CHO).C_6H_5 \rightarrow C_6H_5CO.C({:}CHOH).C_6H_5
\end{aligned}
$$

α-β-Diphenyl-β-phenacylpropionitrile is reduced in the presence of a nickel catalyst at ordinary temperature and under atmospheric pressure to 2,4,5-triphenylpiperidine in 75% yield[31]:

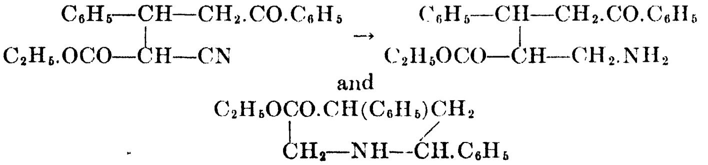


Formylphenylacetonitrile is also reduced to the corresponding aldimine from which the aldehyde is obtained by hydrolysis:



$$\underset{\text{CHO}}{C_6H_5.CH.CN} \rightarrow \underset{\text{CHO}}{C_6H_5.CH.CH{:}NH} \rightarrow \underset{\text{CHO}}{C_6H_5.CH.CHO}$$

Formylnaphthylacetonitrile behaves in a similar manner[32]. γ-Benzoyl-β-phenyl-α-cyanobutyric ethyl ester gives, in small quantity, α-methyl amino-β-phenyl-γ-benzoylbutyric ethyl ester (I), and in larger quantity, 1,3-diphenylpiperidine-4-carboxylic ethyl ester (II)[33]:



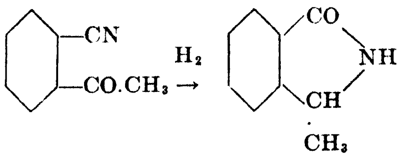
(I)

(II)

At 50–70° and under a pressure of 100–150 atmospheres, formylphenylacetonitrile is reduced to β-phenylpropylamine[34].

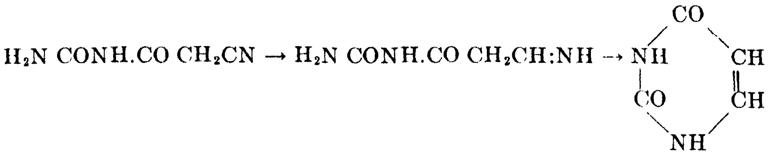
The nitrile group in various homologues of ketoveratronitriles is reduced in preference to the carbonyl group when the reduction is carried out at 35–40° in the presence of Raney nickel; at higher temperatures, aminoalcohols are obtained. In the temperature range 150–200°, a certain amount of cyclic oxides with the same number of carbon atoms as the original nitrile are also formed[35].

o-Cyanobenzophenone may be reduced with hydrogen at ordinary pressure and temperature in presence of catalysts such as palladium or Raney nickel. In an acid medium and by the use of the first named catalyst, the product is 3-methylphthalimidine.

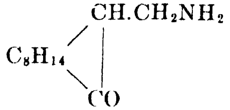


In a neutral medium, there are formed, in addition to 3-methylphthalimidine, other compounds of unknown structure[36].

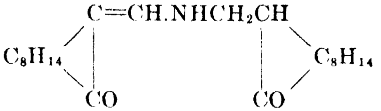
Cyanoacetylurea, reduced at 60–70° in aqueous solution in presence of a nickel catalyst, forms uracil[37]:



α-Cyanocamphor is reduced with hydrogen in the presence of nickel catalyst to α-camphomethylamine,



and an unsaturated secondary base[38],



Reduction of Hydroxynitriles. Cyanohydrins are reduced only to a limited extent in the presence of a nickel catalyst due to the poisoning of the catalyst by hydrocyanic acid formed through the dissociation of the cyanohydrins. Since acylated cyanohydrins do not form hydrocyanic acid, it should be possible to hydrogenate these compounds in the presence of nickel catalyst. Benzoylmandelonitrile has been successfully reduced in this manner, forming a mixture of phenylethylamine and di-(phenylethyl)-amine, and a small amount of N-benzoyl-β-oxyphenylethylamine[39].

The catalytic reduction of mandelonitrile and substituted mandelonitriles proceeds unsatisfactorily at room temperature and under atmospheric pressure[40].

Paal and Gerum[40], who carried out the reduction in the presence of colloidal palladium, identified mono- and dibenzylamines in the product of reduction, as well as ammonia and benzyl alcohol, a result which they ascribed to the fact that the nitrile readily dissociates in solution to benzaldehyde and hydrocyanic acid.

Buck[41] reduced various substituted mandelonitriles in a Burgess-Parr apparatus using Adams platinum oxide catalyst. An alcoholic solution of the nitrile was used, to which was added a slight excess of concentrated hydrochloric acid. The reduction was carried out at ordinary temperature and with 50 pounds of initial hydrogen pressure. The theoretical quantity of hydrogen was rarely absorbed.

The general procedure was to dissolve 0.05 mole of the nitrile in 45 cc of alcohol, and after adding 5.0 cc of concentrated hydrochloric acid, to reduce the solution at room temperature. The amount of catalyst used was 0.1–0.3 gram. The time required for reduction was usually two hours, but occasionally eight to ten hours.

The products of reduction were the corresponding β-phenylethyl- or β-hydroxy-β-phenylethylamine. The yields and products are given in the following table:

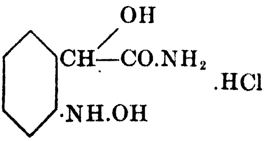
Product	*Melting Point °C*	*% Yield*
o-Methoxy-β-hydroxy-β-phenylethylamine	184	59
o-Chloro-β-hydroxy-β-phenylethylamine	197	41
2,3-Dimethoxy-β-hydroxy-β-phenylethylamine	134	23.5
o-Chlorophenylethylamine	indef. flow at 204°	94
p-Dimethylaminophenylethylamine	froths at 238°	44
p-Methoxyphenylethylamine	210 up	49
3,4-Dimethoxyphenylethylamine	151	52
p-Chlorophenylethylamine	range 195, dec. at 215°	50
Phenylethylamine	217	47

Buck also reduced hydroxymandelonitriles[42] by the same method and found that hydroxy-β-phenylethylamines are formed smoothly. He prepared the following compounds:

	Melting Point °C	*% Yield*
3-Hydroxy-β-phenylethylamine hydrochloride	142	31
4-Hydroxy-β-phenylethylamine hydrochloride	> 260	48
2-Hydroxy-3-methoxy-β-phenylethylamine hydrochloride	175	42
3-Methoxy-4-hydroxy-β-phenylethylamine hydrochloride	froths at 206°	77
3,4-Dihydroxy-β-phenylethylamine hydrochloride	black at 245°	56

When substituted mandelonitriles are reduced with hydrogen in the presence of a platinum catalyst alkyloxy groups, if present, are removed and the benzene ring is hydrogenated[13].

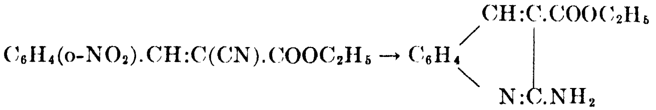
The reduction of o-nitromandelonitrile results, according to Heller, in the formation of a double compound of hydroxylaminomandelonitrile and dihydroxylaminomandelonitrile hydrochloride containing a molecule of water. Reissert and Hessert[44] believe that the compound is hydroxylaminomandelamide hydrochloride:



Reduction of Unsaturated Nitriles. Benzylidenecyanoacetic ester is reduced at ordinary temperature and in the presence of a nickel catalyst to an aldehyde:

$$C_6H_5CH{=}C(CN).COOC_2H_5 + H_2 + H_2O \rightarrow C_6H_5CH_2CH(CHO).COOC_2H_5 + NH_3$$

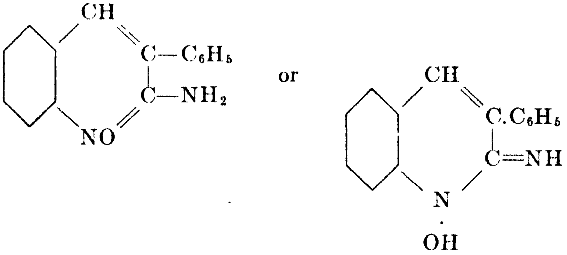
Nitrobenzylidenecyanoacetic ester is reduced under the same conditions to 2-aminoquinoline-3-carboxylic ester:



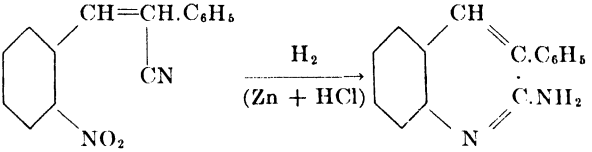
$$C_6H_4(o\text{-}NO_2).CH:C(CN).COOC_2H_5 \rightarrow C_6H_4\begin{cases}CH:C.COOC_2H_5\\ N:C.NH_2\end{cases}$$

In the presence of platinized asbestos, the nitrile is reduced to the N-hydroxyaminoquinoline derivative which, on further reduction with zinc and hydrochloric acid, gives the aminoquinoline.

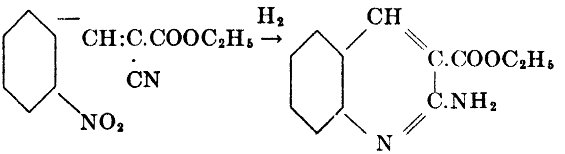
o-Nitro-α-phenylcinnamonitrile is reduced in the presence of platinized silica in ethyl alcohol to 2-amino-3-phenylquinoline-1-oxide[45], m.p. 184–185°:



The reduction of *o*-nitro-α-phenylcinnamonitrile with zinc and hydrochloric acid results in the formation of α-amino-β-phenylquinoline[46], m.p. 156°:



Similarly, the reduction of *o*-nitro-α-cyanocinnamic ethyl ester results in the formation of α-amino-β-carboxylic acid ester[47] m.p. 135°:



The unsaturated bond in acrylonitrile and other unsaturated nitriles of the same type is hydrogenated more readily than the nitrile group, and saturated nitriles may be prepared through the reduction of these nitriles. Stearonitrile may thus be obtained from oleonitrile and, succinonitrile from fumaronitrile[48].

Reduction of Nitrated Aromatic Nitriles. The nitro group in aromatic nitronitriles is reduced upon hydrogenation in the presence of a nickel catalyst at ordinary temperature to an amino group. The nitrile group may or may not be

Nitrile	*Amine Obtained*	*Boiling Point of Amine*		*Yield of Amine, % of Theory*
		°*C*	*Under mm Hg*	
β-Aminopropionitrile........	Trimethylenediamine	138	735	23
β-Diethylaminopropionitrile.	(γ-Diethylaminopropyl)-amine	168	735	54
	Di-(γ-diethylaminopropyl)-amine	107	3	15
β-Ethylaminopropionitrile...	γ-Ethylaminopropylamine	156	735	74
Di-(β-cyanoethyl)-ethylamine	Di-(γ-aminopropyl)-ethylamine	135	20	16
β′-Di-*n*-propylaminopropionitrile.	γ-Di-*n*-propylaminopropylamine	94	20	49
β-Di-*n*-butylaminopropionitrile.	γ-Di-*n*-butylaminopropylamine	121	20	32
β-Pipiperidinopropionitrile ..	γ-Piperidinopropylamine	205	730	68.5
	Di-(γ-piperidinopropyl)-amine	153	2	10
β-Morpholinopropionitrile ..	γ-Morpholinopropylamine	219	733	70.6
	Di(γ-morpholinopropyl)-amine	185	5	10
γ-Diethylaminobutyronitrile	δ-Diethylaminobutylamine	85	18	51
γ-Piperidinobutyronitrile....	δ-Piperidinobutylamine	118–120	25	53.8
	Di-(δ-piperidinobutyl)-amine	220–225	25	32
γ-Morpholinobutyronitrile ..	δ-Morpholinobutylamine	122	20	62
	Di-(δ-morpholinobutyl)-amine	200–202	3	23.8
β-Diethanolaminopropionitrile.	γ-Diethanolaminopropylamine	158	2	40
Bis(β-cyanoethyl)-ether.....	Bis-(γ-aminopropyl)-ether	113	32	29
β-(γ-Diethylaminopropylamino)-propionitrile	γ-(γ′-Diethylaminopropylamino)-propylamine	142–144	25	51
	Di-[γ-(γ′-diethylaminopropylamino)-propyl]-amine	253–260	25	31
β-[Di-(γ′-diethylaminopropyl)-amino]propionitrile...	γ-[Di-(γ′-diethylaminopropyl)-amino]-propylamine	155–165	3	52
β-(β′-Morpholinoethylamino)-propionitrile......	γ-(β′-Morpholinoethylamino)-propylamine	120–123	2	57.5
β-(γ′-Morpholinopropylamino)-propionitrile......	γ-(γ′-Morpholinopropy amino)-propylamine	137–140	1.5	45.2
β(β′-Diethylaminoethoxy)-propionitrile.........	γ-(β′-Diethylaminoethoxy)-propylamine	118–122	25	56.7
	Di-(γ-(β′diethylaminoethoxy)-propyl]-amine	175	3	23.8

Nitrile	Amine Obtained	Boiling Point of Amine		Yield of Amine, % of Theory
		°C	Under mm Hg	
β-(γ′-Diethylaminopropoxy)-propionitrile............	γ-(γ′-Diethylaminopropoxy)-propylamine	130–132	25	57.4
	Di-[γ-(γ′-diethylaminopropoxy)-propyl]-amine	182	3	28.2
β-(δ′-Diethylamino-α-methylbutoxy)-propionitrile.....	γ(δ-Diethylamino-α-methylbutoxy)-propylamine	80–83	2	50.5
	Di-[γ-(δ′-diethylamino-α-methyl butoxy)-propyl]-amine	210–215	3	23
γ-(Methylphenylamino)-propionitrile................	γ-(Methyl phenylamino)-propylamine	171–172	40	63
N-(β-Cyanoethyl)-carbazole.	N-(γ-Aminopropyl)-carbazole	228	3	70.5
N-(β-Cyanoethyl)-tetrahydroquinone..............	N-(γ-Aminopropylamino)-tetrahydroquinoline	132–135	3	82

reduced, depending upon its relative position with respect to the nitro group. The nitrile group is reduced in *p*-nitrobenzyl cyanide; on the other hand, *o*-nitrobenzyl cyanide is reduced to *o*-amino benzyl cyanide, the nitrile group remaining unaffected. *Para-* and *meta-*nitro benzonitriles are reduced to aminoaldimines from which the corresponding aldehydes may be obtained by hydrolysis[49]:

$$NO_2C_6H_4CN \rightarrow H_2N.C_6H_4CH{:}NH \rightarrow H_2NC_6H_4CHO$$

o-Nitrobenzonitrile forms *o*-aminobenzamide: *o*-$H_2NC_6H_4.CONH_2$.

In 1,5-, 2,5- and 1,2-initronaphthonitriles, the nitro group is reduced to an amino group and the nitrile group remains intact[50].

Reduction of Aminonitriles. The hydrochlorides of α-aminonitriles have been hydrogenated in alcohol in the presence of palladium at atmospheric pressure; 1,2-diaminopropane has been obtained in 32% yield from α-aminopropionitrile; 1,2-diamino-2-methylpropane in 53% yield from α-amino*iso*butyronitrile[75].

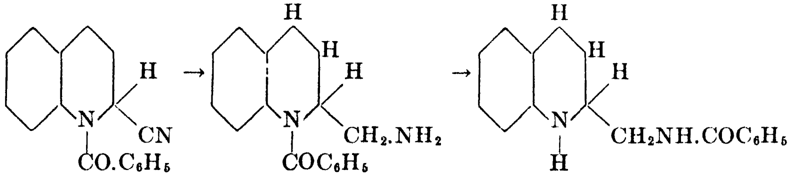
Whitmore and co-workers[77] catalytically reduced β- and γ-aminonitriles in the presence of Raney nickel in the temperature range 90 to 130° under pressures ranging from 67 to 270 atmospheres. The following is a typical case: β-Morpholinopropionitrile was reduced in the absence of a diluent at 120° under a hydrogen pressure of 1400 lb/sq in in twenty minutes, obtaining a 60% yield of γ-morpholinopropylamine. A list of nitriles hydrogenated by Whitmore and co-workers, together with the yields of various amines obtained is given in the table on pages 162–163.

Huber[76] catalytically reduced aminonitriles using Raney nickel as a catalyst, in the presence of a high concentration of ammonia, and obtained nearly quantitative yields of primary amines. Three to four moles of ammonia were present per mole of nitrile, methanol being used as a solvent. The reaction proceeded readily at room temperature under 60 to 200 lb/sq in hydrogen pressure. The average time for complete reaction for 0.5-mole quantities of nitrile ranged from 30 to 80 minutes.

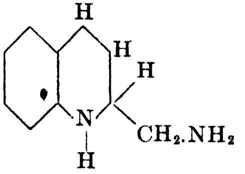
β-Iminonitriles, $RCH_2C(:NH)CH(R).CN$, are reduced readily with hydrogen at temperatures ranging from 75 to 245° in the presence of Raney nickel. The alkyl iminonitriles form diamines, $RCH_2CH.(NH_2).CHRCH_2NH_2$, in 60 to 70% yield. β-Iminobutyronitrile gives only 41% of the diamine. A 27% yield of diamine is obtained from α, γ-diphenyl-β-aminobutyronitrile, the chief product (50%) being $C_6H_5CH_2CH_2CH(NH_2).CH(C_6H_5)CH_3$. It has not been possible to hydrogenate the imino group preferentially[51].

Reduction of Reissert's Compounds. When Reissert's compounds are reduced with sodium and alcohol, the quinoline ring is destroyed. With palladium, reduction proceeds incompletely and a secondary and primary base form. When nickel is used as a catalyst only a primary base is formed.

Rupe and co-workers[52] carried out the reduction with a nickel catalyst at 70–90°, under 100 atmospheres. The reduction proceeds as follows:

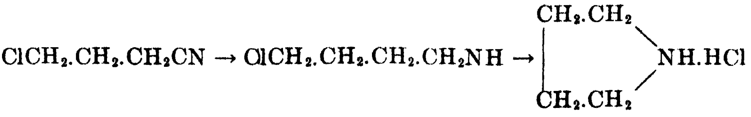


From the final benzoylated product, alcoholic hydrochloric acid liberates the free base



The Reissert compound obtained from *iso*quinoline is similarly hydrogenated to a benzoylated animo compound though, in this case, the reduction must be carried out at a higher temperature and under a higher pressure[53]. Similar results are obtained with the Reissert compound derived from 6-methoxyquinoline[54].

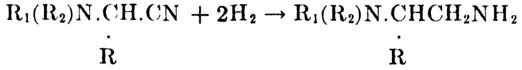
Reduction of Miscellaneous Other Nitriles. The reduction of γ-chlorobutyronitrile results in the formation of pyrrolidine hydrochloride[55]



$$ClCH_2.CH_2.CH_2CN \rightarrow ClCH_2.CH_2.CH_2.CH_2NH \rightarrow \begin{matrix} CH_2.CH_2 \\ | \quad\quad \searrow \\ \quad\quad\quad NH.HCl \\ | \quad\quad \nearrow \\ CH_2.CH_2 \end{matrix}$$

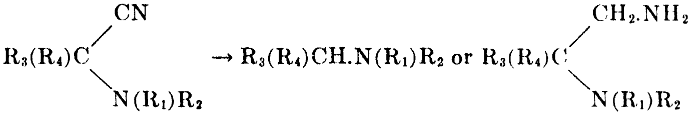
Free γ-chlorobutylamine is unstable, but its salts are stable.

N-Substituted alkylenediamines are prepared from aliphatic aminonitriles by reduction with hydrogen in the presence of hydrogenating catalysts. The primary and secondary amines are formed simultaneously[56].

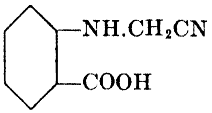


$$R_1(R_2)N.\underset{R}{\overset{}{C}}H.CN + 2H_2 \rightarrow R_1(R_2)N.\underset{R}{C}HCH_2NH_2$$

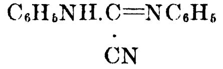
These nitriles in ether solution and in the presence of water are reduced by sodium to diamines and monoamines[57],



The reduction of cyanomethylanthranilic acid



proceeds in a complicated manner; hydrocyanocarbodiphenylimide,

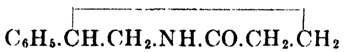


$$C_6H_5NH.\underset{CN}{C}=NC_6H_5$$

forms as an intermediate and is reduced to aniline.

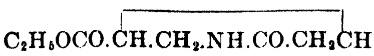
β-Alanine ethyl ester has been obtained by the reduction of ethyl cyanoacetate in the presence of platinum oxide catalyst under a hydrogen pressure of 40 atmospheres[63]. Cyanoacetamide has been reduced in acetic acid solution to alanine amide[93]. β-Alkoxypropionitriles, reduced at 30–150° under 20–250 atm. hydrogen pressure in the presence of Raney nickel, give mono- and di-(-γ-alkoxypropyl) amines[94].

Methyl γ-cyano-γ-phenylbutyrate, $C_6H_5CH(CN).CH_2CH_2COOCH_3$, in alcoholic solution reduced with Raney nickel under 200 atm. hydrogen pressure at 150° for 45 minutes gives 5-phenyl-2-piperidone,



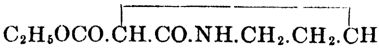
$$C_6H_5.CH.CH_2.NH.CO.CH_2.CH_2$$

m.p. 127–129°, in 88% yield; on further reduction with sodium in warm anhydrous butanol this is converted to 3-phenylpiperidine, m.p. 14–15°. Piperidones have also been obtained through the catalytic reduction of the ethyl esters of γ-cyano-γ-phenylisovaleric, γ-cyano-β,β-dimethyl-γ-phenylbutyric, γ-cyano-β,γ-diphenylbutyric and β-carbethoxy-γ-cyano-γ-phenylbutyric acids[82]. Ethyl α-cyano-γ-carbethoxy-β-phenylbutyrate, $C_2H_5OCOCH_2.CH(C_6H_5).CH(CN)-COOC_2H_5$, hydrogenated 45 minutes at 140° and 2000 lb hydrogen pressure in the presence of Raney nickel gives ethyl 6-keto-4-phenylnipecotate,



$$C_2H_5OCO.CH.CH_2.NH.CO.CH_2CH.C_6H_5$$

in 67% yield. Ethyl 2-keto-4-phenylnipecotate has been prepared from ethyl α, carbethoxy-γ-cyano-β-phenylbutyrate[83]. Ethyl-α-carbethoxy-γ-cyanobutyrate-$CN.CH_2.CH_2CH(COOC_2H_5)_2$, which may be prepared by the condensation of acrylonitrile and sodiodiethylmalonate, reduced in presence of Raney nickel gives ethyl 2-ketonipecotate,

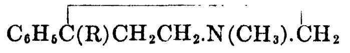


$$C_2H_5OCO.CH.CO.NH.CH_2.CH_2.CH_2$$

3-Substituted 2-ketonipecotates may be prepared similarly from α-substituted α-carbethoxy-γ-cyanobutyric esters. γ-Carbethoxy-α-cyanobutyric ester gives on reduction 5-ketonipecotate[84]. γ,γ-Dicarbethoxy-β-methoxymethylbutyronitrile, $CH_3OCH_2C(CH_2CN).CH(COOC_2H_5)COOC_2H_5$, reduced in the presence of Raney nickel at 155° under 2500 lb hydrogen pressure gives ethyl 2-keto-4-methoxymethylnipecotate[85].

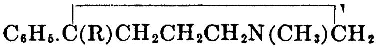
Rosenmund and Pfankuch reduced p-hydroxybenzyl cyanide to di-p-hydroxyphenylethylamine; benzonitrile to benzylamine in acetic acid solution with palladium catalyst in 80% yield; benzyl cyanide to β-phenylethylamine in 73% yield and o-chlorobenzonitrile to benzylamine hydrochloride in 85% yield[57,27].

Pyrrolidine derivatives



$$C_6H_5C(R)CH_2CH_2.N(CH_3).CH_2$$

have resulted from the catalytic reduction of γ-benzylmethylamino-α-phenylbutyronitriles, $C_6H_5C(R)(CN)CH_2CH_2N(CH_3)CH_2C_6H_5$, in the presence of palladium as a catalyst; piperidine derivatives



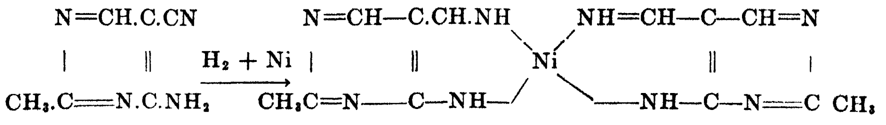
$$C_6H_5.C(R)CH_2CH_2CH_2N(CH_3)CH_2$$

have resulted similarly from the corresponding valeronitriles. R in these compounds[10] represents H or the group $—COOC_2H_5$.

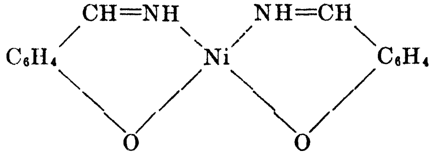
β-Iminonitriles, $RCH_2C(:NH)CH(R)CN$, hydrogenated at temperatures ranging from 75 to 245° in the presence of Raney nickel give the diamines, $RCH_2CH(NH_2).CH(R)CH_2NH_2$, in yields varying between 27 and 70% depending on the character of the hydrocarbon groups R. It has not been possible to hydrogenate the imino group preferentially[51].

Adkins and Whitman[51] attempted to reduce β-iminonitriles partially to β-aminonitriles over Raney nickel or copper chromite catalyst without success. The complete reduction of these nitriles to diamines proceeded readily over Raney nickel.

In the reduction of certain amino- and hydroxynitriles with a nickel catalyst, a nickel-aldmine complex forms[68]. Thus, a nickel-aldimine complex results when 2-methyl-4-amino-5-cyano pyrimidine is reduced with a nickel catalyst:



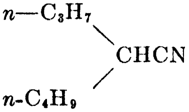
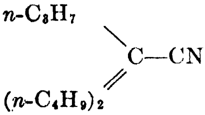
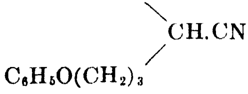
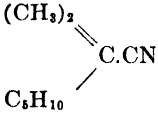
A similar complex forms in the reduction of salicylonitrile:



Aldehydes corresponding to these aldimine complexes have been prepared from these compounds.

The reaction does not stop at this stage, but reduction proceeds further to the formation of the amine. In the case of aminobenzonitrile it has been demonstrated that more complex compounds are also formed.

Reduction of Nitriles with Sodium and Other Reducing Agents. The reduction of nitriles with sodium and alcohol may lead, in the case of some nitriles, to the formation principally of amines; in other cases, to the removal of the CN-group as sodium cyanide. In the following table are presented the results of Walter and McElvain[59]:

Nitrile, R-CN	*Yield of NaCN* %	*Yield of R.H.* %	*Yield of* RCH_2NH_2 %
$n\text{-}C_4H_9.CN$	16	..	76
$(CH_3)_2CH.CN$	24	..	63
$(CH_3)_3C.CN$	33	..	60
 $(n\text{-}C_3H_7)(n\text{-}C_4H_9)CHCN$	6	..	64
 $(n\text{-}C_3H_7)(CN)C{=}(n\text{-}C_4H_9)_2$	10	7	54
C_6H_5CN	84	..	7
$C_6H_5CH_2CN$	88	..	10
 $(C_6H_5)(C_6H_5O(CH_2)_3)CH.CN$	91	89	5
 $(CH_3)_2{=}C(C_5H_{10}).CN$	61	33	23

Nitriles of the type $RR'NCH_2CN$ have been reduced by use of sodium and ethanol or butanol to amines of the type $RR'NCH_2CH_2NH_2$ in yields ranging up to 50%[95].

According to Bamberger and Lodter, benzonitrile and *p*-tolunitrile in ethyl alcoholic solution give principally benzoic and *p*-toluic acids respectively when treated with metallic sodium[60]. Naphthonitrile gives tetrahydronaphthylmethylamine and dihydronaphthalene by the same treatment[61].

Succinonitrile is reduced with sodium and ethyl alcohol to butylenediamine in poor yield, other products such as pyrrolidine forming simultaneously[62].

m-Phenylenediacetonitrile has been reduced with sodium and alcohol to ω,ω'-diamino-*m*-diethylbenzene, $C_6H_4(CH_2CH_2NH_2)_2$, b.p. 165–170° under 20 mm.[86].

Arylidene cyanoacetic acids, $RCH{=}C(CN)COOH$, are readily hydrogenated with sodium amalgam and water to the corresponding saturated cyano- acids, the yields being in excess of 85% of theory[87].

Dibenzylmalononitrile, $(C_6H_5CH_2)_2C(CN)_2$, reduced with sodium and ethyl alcohol gives dibenzylethylamine, $(C_6H_5CH_2)_2CHCH_2NH_2$. Dipropylmalononitrile behaves similarly[89].

Nitriles may be reduced by means of chromous acetate in suspension in alcohol; benzylamine has been obtained in fair yield by this method from benzonitrile. Pyridyl-2-aminomethane and 2,6-dichloropyridyl-4-aminomethane have been obtained similarly from 2-cyanopyridine and 2,6-dichloro-4-cyanopyridine[88].

2-Nitrophenylcinnamonitrile, $NO_2C_6H_4CH{:}C(CN)C_6H_5$, reduced with tin and hydrochloric acid gives 2-amino-3-phenylquinoline[80].

Benzonitrile has been reduced in aqueous-alcoholic solution with coppered magnesium to mono- and dibenzylamines[13]. This nitrile has been reduced to benzylamine with zinc and hydrochloric acid[64].

Formation of Nitriles by Catalytic Dehydrogenation of Amines

The reverse transformation of amines to nitriles by catalytic dehydrogenation is possible in some instances. Thus, isobutyronitrile and isovaleronitrile have been obtained in good yields from isobutylamine and isoamylamine respectively by passing the vapors of these compounds over nickel heated at 320 to 330° or a copper catalyst heated at 400 to 420°. Lower yields of the corresponding nitriles were obtained from the more volatile methyl and ethylamines[65]. Nitriles may be obtained also by the catalytic dehydrogenation of secondary and tertiary amines. Thus, isovaleronitrile has been obtained by passing the vapors of diisoamylamine over a nickel catalyst heated at 320–330°. It appears probable that monoisoamylamine and triisoamylamine are formed as intermediates and that the former is dehydrogenated to the nitrile. The nitrile was obtained from triisoamylamine when the vapors of this compound were passed over a nickel catalyst heated at 360 to 370°, an unsaturated hydrocarbon, presumably isoamylene forming simultaneously. The reaction apparently proceeds as follows[66]:

$$((CH_3)_2CH.CH_2.CH_2)_3N \rightarrow 2(CH_3)_2CH.CH = CH_2 + (CH_3)_2.CH.CH_2.CN + 2H_2$$

The reaction $R\,CH_2NH_2 = R\,CN + 2H_2$ may be forced to the right by adding the vapors of an olefin or benzene to those of the nitrile. The formation of polyalkylamines is reduced to a minimum by adding ammonia as well as an olefin to the vapors of the amine. Benzonitrile has been obtained in excellent yield from benzylamine by this method[96].

Nitriles have also been prepared by passing a mixture of an alcohol and ammonia over a dehydrogenating catalyst in the temperature range 300–400°. It may be assumed that in this process amines are the first product of the reaction[97].

Stephen's Aldehyde Synthesis

Nitriles may be reduced with anhydrous stannous chloride to imines; aldehydes form on hydrolysis of the imines[67]:

$$RCN + SnCl_2 + 3HCl \rightarrow R.CH{:}NH.HCl + SnCl_4$$
$$RCH{:}NH.HCl + H_2O \rightarrow RCHO + NH_4Cl$$

The method is applicable to aliphatic and aromatic nitriles, the yields being nearly quantitative in some cases. *o*-Tolunitrile and *α*-naphthonitrile give low yields of aldehyde due, apparently, to steric hindrance.

Fulton and Robinson[68] prepared *β*-naphthaldehyde in the following manner:

Fifty grams of *β*-naphthonitrile were dissolved in anhydrous ether, the solution was saturated with hydrogen chloride and the nitrile reduced with 250 grams of stannous chloride. The aldimine was then decomposed by distillation with steam. The aldehyde formed was isolated as the bisulfite compound, which was purified by crystallization from 75% alcohol. Thirty-eight grams of pure aldehyde, melting at 58°, were obtained. It is necessary to allow at least two hours for the completion of the reaction.

Williams[69] prepared aldehydes by Stephen's method from various nitriles and showed that the yields varied widely. The yields of aldehyde obtained were as follows:

	Yield, % of Theory
Benzaldehyde	97
β-Naphthaldehyde	91
p-Methylbenzaldehyde	77
Phenylacetaldehyde	33
*Iso*capraldehyde	31
o-Methylbenzaldehyde	9
α-Naphthaldehyde	7
β-Hydroxypropylaldehyde	0

Stephen[67] prepared the following aldehydes:

n-Octaldehyde, b.p.$_{11}$ 65°
Myristaldehyde, m.p. 23°, rapidly polymerizes to a solid, m.p. 65°
Palmitaldehyde, m.p. 34°, polymeride m.p. 73–74°
Stearaldehyde, m.p. 38°, rapidly polymerizes to a solid, m.p. 80°
Benzaldehyde
3,4,5-Trimethoxybenzaldehyde, m.p. 98°
o-Tolualdehyde, b.p.$_{10}$ 94
p-Tolualdehyde, b.p.$_{10}$ 106
o- and *p*-Chlorobenzaldehydes
Phenyl-, *p*-chlorophenyl- and *p*-tolyl acetaldehydes
Cinnamaldehyde

β-Phenylpropaldehyde
α-Naphthaldehyde

King and co-workers[70] prepared γ-phthalimidobutyraldehyde from the corresponding nitrile in good yield. The aldehyde polymerizes rapidly.

Making use of Stephen's method, Law and Johnson[71] prepared *p*-Ethoxy-*p'*-aldehydediphenyl sulfide, $C_2H_5OC_6H_4.S.C_6H_4.CHO$, m.p. 83°; *p*-Methyl-*p'*-aldehydediphenyl sulfide, $CH_3.C_6H_4.S.C_6H_4CHO$, m.p. 69°.

Wood and Stanfield[72] prepared 2,7-naphthaldehyde from 2,7-naphthalene dinitrile. The yield of aldehyde was 24.3% of theory.

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Chapter 9

Reaction of Hydrocyanic Acid and Alkali Cyanides with Aldehydes and Ketones: Reactions of Cyanohydrins

Aldehydes and ketones react with hydrocyanic acid to form cyanohydrins

$$R_1R_2.CO + HCN \rightarrow R_1R_2C(OH)CN$$

The reaction is accelerated by small amounts of bases. For example, in the absence of substances of basic nature, pure hydrocyanic acid and pure acetaldehyde do not react at a rapid rate even at 100°[1], although the fact that aldehyde cyanohydrin is formed on keeping the mixture at 25 to 30° for eight days shows that the reaction proceeds slowly. Reaction takes place rapidly at ordinary temperature when substances of basic character, such as sodium hydroxide or ammonia, are added. Since the greater part of the base combines with hydrocyanic acid, the concentration of the free base in the liquid is quite low. The rate of reaction is also dependent on the character of the aldehyde or ketone. Aldehydes, in general, react more rapidly than ketones. Mixed aromatic aliphatic ketones react slowly and purely aromatic ketones do not form cyanohydrins with hydrocyanic acid.

Cyanohydrins may be prepared by the addition of an acid to a mixture of the aldehyde and a solution of alkali cyanide. Another method of preparation of aldehyde cyanohydrins consists in the addition of a solution of an alkali cyanide to that of the bisulfite compound of the aldehyde:

$$RCH(OH)SO_3Na + NaCN \rightarrow RCH(OH)CN + Na_2SO_3$$

Dissociation of Cyanohydrins. The reaction between aldehydes or ketones and hydrocyanic acid is reversible, and the extent to which the reaction proceeds is different for the different carbonyl compounds.

Alkalies decompose aldehyde and ketone cyanohydrins to alkali cyanide and the corrsponding carbonyl compound, as a consequence of the reversible character of the reaction.

The dissociation constants of various cyanohydrins are presented in the table on following page:

$$K = \frac{[\mathrm{HCN}][\mathrm{R_1R_2CO}]}{[\mathrm{R_1R_2C(OH)CN}]}$$

Cyanohydrin of	*Temp., °C*	*Dissoc. Constant* $K \times 10^2$
Acetaldehyde	20	0.28
Propionaldehyde	25	0.21
Butyraldehyde	25	0.096
*Iso*butyraldehyde	25	0.096
Acetone	20	3.05
Methyl ethyl ketone	20	2.65
n-Propyl methyl ketone	20	3.55
*Iso*propyl methyl ketone	20	3.20
n-Butyl methyl ketone	20	1.55
tert.-Butyl methyl ketone	20	3.10
Monochloroacetone	20	2.15
Benzaldehyde	20	0.47
o-Nitrobenzaldehyde	20	0.07
m-Nitrobenzaldehyde	20	0.27
p-Nitrobenzaldehyde	20	1.81
o-Chlorobenzaldehyde	20	0.10
m-Chlorobenzaldehyde	20	0.25
p-Chlorobenzaldehyde	20	0.49
o-Methoxybenzaldehyde	20	0.26
m-Methoxybenzaldehyde	20	0.43
p-Methoxybenzaldehyde	20	3.12
o-Hydroxybenzaldehyde	20	1.67
m-Hydroxybenzaldehyde	20	0.48
p-Hydroxybenzaldehyde	20	7.66
m-Methylbenzaldehyde	20	0.60
p-Methylbenzaldehyde	20	1.03
4-Me-4MeO-benzaldehyde	20	2.00
3-Me-4MeO-benzaldehyde	20	3.82
p-Di-Me-aminobenzaldehyde	20	39.0
Benzyl methyl ketone	20	2.15
β-Phenyl ethyl ketone	20	3.50
β-Phenyl propyl ketone	20	3.60
Methyl phenyl ketone	20	130
Ethyl phenyl ketone	20	60
n-Propyl phenyl ketone	20	90
n-Butyl phenyl ketone	20	115
n-Amyl phenyl ketone	20	130
n-Hexyl phenyl ketone	20	145
*Iso*propyl phenyl ketone	20	25
*Iso*butyl phenyl ketone	20	155
*Iso*amyl phenyl ketone	20	155
*Iso*hexyl phenyl ketone	20	125
tert.-Butyl phenyl ketone	20	9
Cyclohexyl phenyl ketone	20	40
Cyclobutanone	20	4.54
Cyclopentanone	20	1.49
Cyclohexanone		0.09

Cyanohydrin of	*Temp., °C*	*Dissoc. Constant $K \times 10^2$*
2-Methylcyclohexanone		0.06
3-Methylcyclohexanone		0.30
4-Methylcyclohexanone		0.13
Cycloheptanone		7.96
Cyclooöctanone	20	83.9
Cyclononanone	20	117.
Cyclotetradecanone	20	10.8
Cyclopentadecanone	20	8.8
Cyclohexadecanone	20	12.4
Cyclotricontanone	20	3.3
Menthone		6.54
α-Hydrindone		610.0
α-Ketotetrahydronaphthalene		806.0
Fluorenone		146.0

Baker and Hemming[2] determined the dissociation constant of a number of *p*-substituted mandelonitriles in 95% ethyl alcohol. Their results are presented in the following table:

Cyanohydrin of	*Dissociation Constant, $K \times 10^3$*	
	At 20°C	*At 35°C*
Benzaldehyde	4.47	8.80
p-Methylbenzaldehyde	8.98	20.32
p-Ethylbenzaldehyde	8.18	17.39
*p-Iso*propylbenzaldehyde	8.04	16.50
p-tert. Butylbenzaldehyde	7.49	15.04

Lapworth and Manske[3] determined the dissociation constant of cyanohydrins in 96% ethyl alcohol, using tripropylamine as a catalyst. The results indicate that specific solvent effects are absent.

Water exerts a dissociative effect on cyanohydrins. Thus, in aqueous solution containing 0.1 gm mole of hydrocyanic acid and acetone, combination takes place to the extent of 42.1% as a maximum at 25°. Under the same conditions, hydrocyanic acid and acetaldehyde combine to the extent of 76.6%. In 98.13% aqueous alcohol, acetone and hydrocyanic acid combine to the extent of 52.9%. At 25° and in the absence of water, hydrocyanic acid and acetone combine to the extent of 88.6%, and hydrocyanic acid and acetaldehyde to the extent of 99.55%[4]. Wirth[14a] showed that in aqueous solutions, the dissociation of benzaldehyde cyanohydrin increases with dilution and with temperature.

Stewart and Fontana[5] determined the dissociation constant of acetone cyanohydrin in various solvents at 25°, using triethanolamine as a catalyst. The results obtained by these investigators are given in the table on page 176.

Certain general conclusions may be drawn from the work on the dissociation of cyanohydrins:

The replacement of a hydrogen atom of methyl alkyl ketone cyanohydrin in the alpha position by a methyl group usually increases the stability of the cyanohydrin; the replacement of a beta hydrogen by methyl usually has the slightly opposite effect.

Solvent	*Total Concentration of Cyanohydrin*	*Constant K*
Methyl alcohol	0.122	0.052
	0.058	0.054
Ethyl alcohol	0.372	0.032
	0.096	0.031
Butyl alcohol	0.121	0.023
	0.060	0.023
2-Methylpropyl alcohol	0.159	0.025
1,1-Dimethylethyl alcohol	0.104	0.029
Acetone	0.112	0.008

The cyanohydrins of phenyl alkyl ketones are relatively stable. There is a marked increase in stability from acetophenone to propiophenone and then a gradual but persistent decrease as the series is ascended.

The dissociation of cyanohydrins is catalyzed by amines in all solvents. The catalyzed reaction is immeasurably rapid in water and in the lower alcohols; measurable in butyl alcohol and non-polar solvents, and extremely slow in dioxane.

The degree of dissociation is increased by amines in water; is totally unaffected in various alcohols and in acetone, and is decreased in carbon tetrachloride, benzene, chloroform and dioxane.

REACTION OF HYDROCYANIC ACID WITH ALDEHYDES AND KETONES

Reaction with Aliphatic Aldehydes

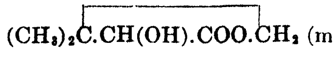
Formaldehyde reacts readily with hydrocyanic acid. Reaction proceeds at room temperature when hydrocyanic acid is added to 40% formaldehyde, especially in the presence of a small amount of base in solution; sodium acetate serves well in this case[6].

The reaction between *acetaldehyde* and hydrocyanic acid proceeds at ordinary temperature in the presence of a base[7].

In dilute aqueous solution containing 0.1 gm molecular equivalents of acetaldehyde and hydrocyanic acid, these compounds combine in the presence of a trace of alkali at 25° to the extent of 76.6%[8].

*Iso*butyraldehyde cyanohydrin has been prepared from *isobutyraldehyde* and hydrocyanic acid[9]. *Crotonaldehyde* cyanohydrin and *acrolein* cyanohydrin have also been prepared from the corresponding aldehydes and hydrocyanic acid[10]. Hydroxycaprylonitrile, $C_6H_{13}CH(OH)CN$, has been prepared from *oenanthol* and hydrocyanic acid. The amide has been prepared from the nitrile[11]. The nitrile has been converted to aminonitrile.

The cyanohydrin of *methyloldimethylethanal*, $(CH_3)_2C(CH_2OH)CH(OH)CN$, has been made from the aldehyde and hydrocyanic acid; it is converted on hydrolysis to the γ-lactone[145]



$$\overline{(CH_3)_2C.CH(OH).COO.CH_2}$$ (m.p. 55°, b.p.$_{11}$ = 115–117°)

α-Chlorocrotonaldehyde cyanohydrin, $CH_3\text{-}CH{:}CCl.CH(OH)CN$, b.p.$_{26}$ 137–138°, has been prepared in good yield from *α-chlorocrotonaldehyde*[12]. Chloral cyanohydrin,

$Cl_3CCH(OH)CN$, has been prepared from *chloral* and hydrocyanic acid[13]. Potassium hydroxide reacts with the compound to form dichloroacetic acid[14]:

$$Cl_3C.CH(OH)CN + KOH \rightarrow Cl_2CH.COOH + KCl + HCN$$

Methylethylacrolein cyanohydrin, $C_2H_5.CH:C(CH_3)CH(OH)CN$, has been prepared from methylethylacrolein and hydrocyanic acid[15].

β-Chlorolactonitrile, $Cl.CH_2.CH(OH)CN$, has been prepared from *chloroacetaldehyde*[16].

Glyoxal reacts with hydrocyanic acid to form mesotartaric nitrile and tartaric dinitrile. The compound exists in two isomeric forms, the meso- and racemic-forms[17].

Aldol in ether solution condenses, at −5 to 0°, with a molecular equivalent of hydrocyanic acid generated *in situ* by the interaction of potassium cyanide and hydrogen chloride, to form α, α-dihydroxyvaleronitrile[18]. Crotonchloral cyanohydrin has also been prepared. Both chloral- and crotonchloral cyanohydrins have been hydrolyzed to the corresponding hydroxy acids.

Some physical constants of aldehyde cyanohydrins prepared by Ultee[19] are given in the following table:

Cyanohydrin of	*Boiling Point*		*Density*	*At °C*	*Refractive Index n_D*	*At °C*
	°C	*Under mm Hg*				
Formaldehyde	....	....	1.103	19	1.4118	19
Acetaldehyde	90	17	0.9959	14	1.40644	14
Propionaldehyde	102–103	23	0.9690	15	1.41745	15
n-Butyraldehyde	110.5–111	20.5	0.9434	15.5	1.42265	15.5
*Iso*butyraldehyde	106–106.5	22	0.9453	16	1.42215	16
Oenanthaldehyde	143.5–144	19	0.9099	14.5	1.43787	14.5

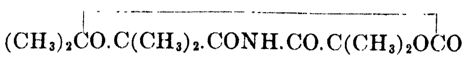
Reaction with Aliphatic Ketones

The reaction between acetone and hydrocyanic acid proceeds at ordinary temperature, though at a slower rate than that between aldehydes and hydrocyanic acid.

Acetone cyanohydrin may be prepared through the interaction of acetone and hydrocyanic acid in the presence of a basic substance, such as sodium hydroxide or cyanide[20]. Reaction takes place rapidly in the presence of 0.1 to 0.2% of the base which may be dissolved in hydrocyanic acid and an equivalent quantity of acetone gradually added. To obtain a light-colored product, the reaction should be carried out at a low temperature. In order to avoid the accumulation of unreacted acetone the liquid should be heated occasionally. The cyanohydrin may be recovered in a pure form by fractionally distilling the liquid under vacuum after carefully neutralizing the base with a mineral acid. Acetone cyanohydrin boils at 82° under 23 mm of pressure.

Acetone cyanohydrin condenses with acetone in the presence of hydrogen chloride on heating on a water bath, forming the compound $(CH_3)_2C(OH)OC(CH_3)_2.CN$, needles, melting at 162–163°. Ethyl methyl ketone, condensing with acetone cyanohydrin under the same conditions, forms a similar compound, $(CH_3(C_2H_5).C(OH)O.$-$C(CH_3)_2.CN$, melting at 115–117°[21].

The cyanohydrin is capable of absorbing 0.66 mole of hydrogen chloride in the cold; after the addition of water, a crystalline product, $C_{12}H_{19}O_5N$, m.p. 193°, forms. The probable structure of this compound is



$$(CH_3)_2CO.C(CH_3)_2.CONH.CO.C(CH_3)_2OCO$$

A compound of the composition[22], $C_8H_{14}O_2N_2.HCl.H_2O$, has also been isolated.

When acetone is heated with a solution of potassium cyanide in alcohol saturated with hydrogen chloride, mesitonic acid, $C_7H_{12}O_3$, mesitic acid, $C_8H_3O_3N$, and the nitrile of phorone acid, $C_{11}H_{18}O_5$, form[23].

Ethyl vinyl ketone, $CH_2{:}CH.COC_2H_5$, reacts with one molecule of hydrocyanic acid to form β-propionyl propionic nitrile, or with two molecules to form the compound[24], $CH_2(CN).CH_2.CH(OH).(CN).C_2H_5$.

Acetonylacetone reacts with two molecules of hydrocyanic acid to form dihydroxydimethyladiponitrile[25], $CH_3C(OH)(CN).CH_2.CH_2.C(OH)(CN).CH_3$.

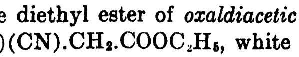
Methyl acetylacetone reacts with hydrocyanic acid generated *in situ* by the interaction of potassium cyanide and hydrogen chloride, to form dihydroxytrimethylglutaric nitrile[26], $CH_3C(OH)(CN).CH(CH_3)C(OH)(CN).CH_3$.

The dicyanohydrin of *benzoylacetone*, $C_6H_5C(OH)(CN).CH_2C(OH)(CN).CH_3$, has been prepared from the diketone[27].

Diacetyl reacts with hydrocyanic acid to form diacetyl cyanohydrin[28], $CH_3.C(OH)$-$(CN).C(OH)(CN).CH_3$, m.p. 110°. On heating the cyanohydrin for a short time with concentrated nitric or hydrochloric acid, it is converted to an isomer, melting at 162°. This is probably the racemic form; the low melting compound being the meso-isomer[29]. *Sym.-tetrachlorodiacetyl* also gives a dicyanohydrin, as well as a monocyanohydrin[30]. The cyanohydrin of acetoacetic ester $CH_3C(OH)(CN).CH_2COOC_2H_5$, has been prepared in 97% yield from the bisulfite compound of acetoacetic ethyl ester[31]. The cyanohydrin has also been prepared by Demarcay and Morris from hydrocyanic acid and ethyl acetoacetate[32]. The cyanohydrin of methylacetoacetic ethyl ester, $CH_3C(OH)(CN).CH(CH_3)COOC_2H_5$, has been prepared in a similar manner[33].

The product of the interaction of hydrocyanic acid and pyruvic acid, $CH_3CO.$-$COOH$, is probably lactonitrile; this is indicated by the fact that lactic acid is obtained by the hydrolysis of the product with hydrochloric acid[34]. Potassium pyruvic cyanohydrin, $CH_3C(OH)(CN).COOK$, m.p. 151°, has been prepared by adding pyruvic acid dropwise, to a suspension of potassium cyanide in boiling alcohol[35]. The free cyanohydrin melts at 87°.

Potassium cyanide in concentrated aqueous solution reacts with levulinic acid, $CH_3COCH_2CH_2COOH$, to form levulinic cyanohydrin, which undergoes internal condensation giving glutaconic nitrile[154],



$$CH_3C(CN)CH_2.CH_2CO.O$$

The dicyanohydrin of the diethyl ester of *oxaldiacetic acid* (ketipic acid), C_2H_5-$OCO.CH_2C(OH)(CN).C(OH)(CN).CH_2.COOC_2H_5$, white plates, m.p. 164°, has been prepared by the action of "nascent" hydrocyanic acid on the diketo acid ester at ordinary temperature. The reaction is complete only after several days. The two nitrile groups in the cyanohydrin are selectively hydrolyzed to carboxyl groups with dilute alcoholic potassium hydroxide[36].

Cyclopropyl methyl ketone cyanohydrin,

$$\overline{\mathrm{CH_2CH_2CH}}\mathrm{.C(OH)(CN).CH_3}\ (\mathrm{b.p._3} = 94\text{–}96°)$$

has been prepared from *cyclopropyl methyl ketone*[37].

Monochloroacetone cyanohydrin has been prepared from *monochloroacetone* and hydrocyanic acid by heating an alcoholic solution of the compounds under a reflux condenser for 24 hours[38]. The cyanohydrin may be obtained in good yield by adding hydrocyanic acid to monochloroacetone, to which a little potassium carbonate has been added. The reaction proceeds readily at 30–35° and is complete within an hour[39].

Good yields of cyanohydrins are obtained by the action of alkali metal cyanides on the bisulfite compound aldehydes or ketones. With the bisulfite compound of acetone, a 96% yield of cyanohydrin has been obtained[40].

Sym.-dichloroacetone cyanohydrin has been prepared from *sym.*-dichloroacetone and aqueous hydrocyanic acid. The compound has been hydrolyzed with concentrated hydrochloric acid to *sym.*-dichloro-α-hydroxy isobutyric acid; from the potassium salt of this compound, the dicyanide has been prepared by reaction with potassium cyanide. Hydrolysis of this compound with concentrated hydrochloric acid gives *citric acid*[41].

Ketene reacts with hydrocyanic acid to form the compound, $C_5H_5O_2N$, which is probably α-acetoxyacrylonitrile; its formation may be explained by assuming that ketene cyanohydrin is first formed and is then acetylated by ketene[42]:

$$\mathrm{CH_2{=}CO + HCN \rightarrow CH_2{=}C(CN)OH}$$
$$\mathrm{CH_2{=}C(CN)OH + CH_2{=}CO \rightarrow CH_2{=}C(CN)OCOCH_3}$$

Acetylmalonitrile, $\mathrm{CNCH_2.CH(CN)OCOCH_3}$, results when the reaction between ketene and hydrocyanic acid is carried out in an inert solvent at −5 to 35°, in the presence of tertiary aromatic or hydroaromatic amines or, tertiary amides[79]. At 350° over charcoal or pumice catalyst acetyl cyanide is formed[156].

Some physical constants of ketone cyanohydrins, prepared by Ultee[43], are given in the following table: (Constants of other cyanohydrins, table pp. 180 and 181.)

Cyanohydrin of	*Boiling Point*		*Density*	*At °C*	*Refractive Index n_D*	*At °C*
	°C	*Under mm Hg*				
Acetone	82	23	0.932	19	1.40002	19
Methyl ethyl ketone	....	....	0.9303	19	1.41525	19
Diethyl ketone	97.5	18.5				
Methyl propyl ketone	100	21	0.9166	13	1.42585	19
Methyl *iso*propyl ketone	97	9	0.9334	13	1.42755	13
Methyl butyl ketone	114	21	0.9102	13.5	1.42915	13.5
Methyl *iso*butyl ketone	109	24				
Dipropyl ketone	119	21	0.9077	18	1.43366	18
Monochloracetone	110	22	1.2027	15	1.45362	11
Cyclohexanone	125.5–126	17.5				
Ethyl pyruvate	105–105.5	19	1.0988	16	1.42435	17
Ethyl acetoacetate	127–128	16.5	1.0886	13.5	1.43557	13.5

Constants of a number of additional cyanohydrins, with references, are given in the following table:

	Density	*At °C*	*Boiling Point °C*	*Under mm*	*Melting Point °C*	*Reference*
Chloral cyanohydrin, $Cl_3C.CH(OH)CN$	......	..	215–220	.....	61	
Ethylene cyanohydrin, $HOCH_2CH_2CN$	1.0588	0	220–222	723.5		
β-Hydroxybutyronitrile, $CH_3CH(OH)CH_2.CN$	1.0134	9	220–221	757		
Butyrchloral cyanohydrin, $CH_3CHCl.CCl_2CH(OH)CN$.	......	..	230(dec.)	.....	101–102	Pinner, A. and Bischoff, C. *Ann.*, **179**, 97 (1875) Pinner, A. and Klein, F., *Ber.*, **11**, 1488 (1878)
Pinacolin cyanohydrin, $(CH_3)_3C.C(CH_3)(OH)CN$.	......	..	....	.....	103–104	Henry, L. *Compt. rend.*, **143**, 20 (1906)
Oenanthol cyanohydrin, $CH_3(CH_2)_5CH(OH)CN$.	0.9048	17	143.5–144	19	−10	Erlenmeyer, E. and Siegel, O. *Ann.*, **177**, 103 (1875)
Dipropylketone cyanohydrin, $(CH_3CH_2CH_2)_2C(OH)CN$.	0.9077	18	119–120	21	.. ..	Ultee, A. J. *Rec. trav. chim.*, **28**, 7 (1909); *Ber.*, **39**, 1858 (1906)
Tridecanol cyanohydrin, $CH_3(CH_2)_{11}CH(OH)CN$.	......	..	....	.....	44.5	LeSueur, H. R. *J. Chem. Soc.*, **87**, 1904 (1905)
Myristinaldehyde cyanohydrin, $CH_3(CH_2)_{12}CH(OH)CN$.	......	..	....	....	50.5	LeSueur, H. R., *ibid.*, **87**, 1901 (1905)
Pentadecanal cyanohydrin, $CH_3(CH_2)_{13}CH(OH)CN$	......	..	52.5–53.5	....	....	LeSueur, H. R., *ibid.*, **87**, 1897 (1905)
Palmitinaldehyde cyanohydrin, $CH_3(CH_2)_{14}CH(OH)CN$.	......	..	60–61	.....	....	LeSueur, H. R., *ibid.*, **87**, 1893 (1905)
Margarinaldehyde cyanohydrin, $CH_3(CH_2)_{15}CH(OH)CN$.	......	..	61–62.5	.....	....	LeSueur, H. R. *ibid.*, **85**, 834 (1904)
Acrolein cyanohydrin, $CH_2{:}CH.CH(OH)CN$	1.009	15	93–94	16–17	....	deBruyn, L., *Rec. trav. chim.*, **4**, 223 (1885) van-derSleen, *ibid.*, **21**, 211 (1902)

	Density	At °C	Boiling Point °C	Under mm	Melting Point °C	Reference
Crotonaldehyde cyanohydrin, $CH_3.CH:CH.CH(OH)CN$	......	..	132–134	15	....	Fittig, R. and Schaak, M. F., *Ann*, **299**, 34(1898)
*Iso*butyraldol cyanohydrin, $(CH_3)_2CH.CH(OH)-C(CH_3)_2CH(OH)CN$	......	..	....	.....	157–158	
Glyoxal cyanohydrin, CNCH(OH)CH(OH)CN	......	..	....	.....	131	
Tetrachlorodiacetyl-bis-cyanohydrin, $Cl_2CH.-C(OH)(CN).CH(OH)(CN).CHCl_2$.	......	..	....	.....	135–137	Levy S. and Witte, F. C., *Ann.*, **254**, 98 (1889)
Dibromodiacetyl-bis-cyanohydrin, $BrCH_2.C(OH)-(CN).C(OH)(CN).CH_2Br$.	......	..	....	.....	177(dec.)	Keller, H. F. and Maas, P., *Chem. Zentr.*, **1898** I, 24. *J. Frankl. Inst.* **144** 379 (1897)
Acetylacetone-bis-cyanohydrin, $CH_3C(OH)(CN)-CH_2C(OH)(CN)CH_3$.	......	..	....	.....	134–136(dec.)	Zelinsky, N., *Ber.*, **24**, 4007 (1891)
Propionylacetone-bis-cyanohydrin, $CH_3C(OH)-(CN)CH_2C(OH)(CN)C_2H_5$.	......	..	....	...	145(dec.)	Fittig, R. and Panayeff, J. v., *Ann.*, **353**, 24 (1907)
Butyrylacetone-bis-cyanohydrin, $CH_3C(OH)-(CN).CH_2.C(OH)(CN)C_3H_7$.	......	..	....	....	137	Fittig, R. and Panayeff, J. v. *ibid.*, **353**, 36 (1907)
Ethylacetylacetone-bis-cyanohydrin, $CH_3C(OH)-(CN)CHCC_2H_5).C(OH)(CN)CH_3$.	......	..	....	....	139	Fittig, R. and Peters, W. *ibid.*, **353**, 39 (1907)
Ethylacetylacetone bis-cyanohydrin, $CH_3C(OH)-(CN)CH(C_2H_5).C(OH)(CN)CH_3$, low melting.	......	..	....	.....	124	Fittig, R. and Peters, W. *ibid.*, **353**, 41 (1907)
Tetrachlorodiacetyl cyanohydrin, $Cl_2.CH.CO.-C(OH)(CN)CHCl_2$.	......	..	....	.....	110–111	Levy, S. and Witte, F. C. *ibid.*, **254**, 100 (1889)

Reaction with Sugars

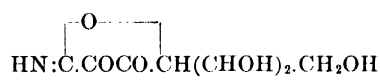
Fructose cyanohydrin has been obtained from *fructose* syrup and concentrated aqueous hydrocyanic acid[44]. *d-Glucose* and *l-arabinose* also react with hydrocyanic acid to form cyanohydrins[45]. The products of partial hydrolysis, α-glucoheptoic lactone and *l*-mannoic acid amide, have been isolated.

Glucose cyanohydrin has been prepared from pentacetylglucose cyanohydrin by hydrolysis with sulfuric acid. Hydrolysis is carried to the point where half of the nitrile is hydrolyzed to glucose carboxylic acid, the other half is then obtained as the pure glucose cyanohydrin in a crystalline form, m.p. 115–120° (dec.)[46].

l-Gluconic acid is formed by the saponification of the reaction product of *l*-xylose and hydrocyanic acid[47]. *l-Lyxose,* $HOCH_2(CHOH)_3.CHO$, reacts with hydrocyanic acid to form a cyanohydrin; *mannose* gives mannose nitrile[48]; *d-galactose* gives the stereo-isomeric α- and β-galahepton nitriles[49]. *d-Fructose,* reacting with hydrocyanic acid forms fructose nitrile[50]; *d-mannoheptose* gives the nitrile of *d*-mannoöctonic acid[51].

In preparing cyanohydrins of aldoses and ketoses, the addition of a drop of ammonia to the anhydrous hydrogen cyanide is found to accelerate the reaction considerably[52].

Potassium cyanide reacts with *d*-glucosone in aqueous solution in the presence of calcium chloride to form a cyanohydrin, $CH_2OH(CHOH)_3CO.CH(OH)CN$, which is probably cyclized to form iminogluco-ascorbic acid; it is oxidized with iodine to a diketoimide,

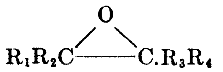


$$HN{:}\overset{\lceil\text{---O---}\rceil}{C.COCO.C}H(CHOH)_2.CH_2OH$$

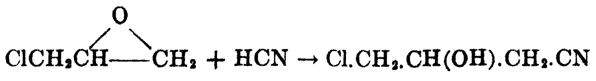
and this is readily hydrolyzed with cold dilute acids to the corresponding lactone. *d*-Galactosone also reacts with KCN under the same conditions to form a cyanohydrin[53]. Ascorbic acid has been prepared from oson cyanohydrins[54].

Reaction with Epoxy Compounds

Ethylene oxide and other epoxy compounds of the type,



react very slowly with hydrocyanic acid in the cold. The reaction proceeds more rapidly in the presence of an alkaline reagent. Thus, if a mixture of *epichlorhydrin* and hydrocyanic acid, containing a little potassium cyanide, is allowed to stand for a few days, chloro-4-hydroxybutyronitrile is obtained in 85% yield[55].



The reaction of epoxy compounds with hydrocyanic acid is accelerated by heat, and rapid combination may be brought about by heating the two compounds under pressure in the presence of a small quantity of a basic substance.

β-Hydroxynitriles, such as ethylene cyanohydrin and propylene cyanohydrin, may be readily dehydrated to unsaturated nitriles. Thus, from ethylene cyanohydrin *acrylic nitrile* may be readily obtained by catalytic dehydration in the presence of aluminum oxide.

Reaction with Aromatic Aldehydes

Benzaldehyde cyanohydrin has been prepared by the action of so-called nascent hydrocyanic acid on *benzaldehyde*, by adding sulfuric acid to a mixture of benzaldehyde and a solution of an alkali cyanide[56].

Salicylaldehyde cyanohydrin has been prepared from *salicylaldehyde* and hydrocyanic acid. The nitrile has been converted to 2-hydroxymandelic acid by treatment with concentrated hydrochloric acid[58]. The acid, which has not been isolated in a cystalline form, has been converted to 3-hydroxy-2-(3)-benzofuranone, m.p. 107–108°[59]. 4-Hydroxymandelonitrile, m.p. 99–102°, has been prepared similarly and converted to 4-hydroxymandelic acid. The hydrate of the acid melts at 83–84°, the anhydrous acid at 109.5–110.5°[59].

p-Nitrobenzaldehyde cyanohydrin has also been obtained from *p-nitrobenzaldehyde* and nascent hydrocyanic acid[60]. Anisaldehyde cyanohydrin (*p*-methoxymandelonitrile), m.p. 66–67°, has been prepared by the same method[61]. The cyanohydrin of *o-chlorobenzaldehyde* has also been prepared by the direct action of the hydrocyanic acid on the aldehyde. The cyanohydrin readily yields the corresponding mandelic acid on heating with concentrated hydrochloric acid[62].

p-Dimethylaminobenzaldehyde cyanohydrin has been prepared from the aldehyde and hydrocyanic acid in the presence of a trace of calcium hydroxide as a catalyst in 59% yield; it is a white solid melting at 110–113°. The amide of the corresponding acid was obtained by hydrolyzing the cyanohydrin with cold concentrated sulfuric acid[63].

Buck[64] prepared the following cyanohydrins from the corresponding aldehydes in the yields indicated:

	Yield % *of Theory*
o-Methoxymandelonitrile	43–65
p-Methoxymandelonitrile	62
o-Chloromandelonitrile	73
p-Chloromandelonitrile	81
2,3-Dimethoxymandelonitrile	54
3,4-Dimethoxymandelonitrile	78
Carbethoxymandelonitrile b.p.$_8$ = 136°	
p-Methoxycarbethoxymandelonitrile b.p.$_2$ = 170°	
o-Chlorocarbethoxymandelonitrile b.p.$_{4.4}$ = 145°	

Vanillin cyanohydrin has been prepared from *vanillin* and hydrocyanic acid in the presence of KCN as a catalyst[65].

Benzaldehyde cyanohydrin and substituted benzaldehyde cyanohydrins have also been prepared from the bisulfite compound of the aldehyde. This method is usually preferred because the reaction proceeds readily, and the cyanohydrin is obtained in good yield[66].

Buck proceeded as follows:

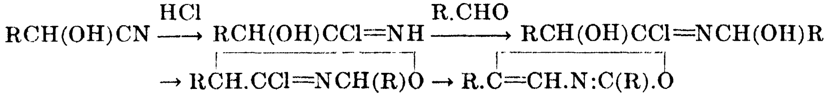
The aldehyde was dissolved in the bisulfite solution heated to 50° and, after cooling to 0°, concentrated potassium cyanide solution was added drop by drop while the solution was agitated. The product was extracted with ether, the ether extract was washed successively with bisulfite solution and water, then dried with calcium chloride, and finally the ether was evaporated off.

Cyanohydrins of *m*-hydroxy-, *p*-acetoxy-3-hydroxy-4-methoxy-, and 4-hydroxy-3-methoxybenzaldehyde have been prepared by this method[67]. *o*-Nitromandelonitrile has been similarly prepared from the bisulfite compound of *o*-nitrobenzaldehyde[68].

In the preparation of benzaldehyde cyanohydrin from the bisulfite compound of benzaldehyde and potassium cyanide, di-(alpha-cyanobenzyloxy)-phenyl-methane, $C_6H_5CH.(OCH(CN).C_6H_5)_2$, m.p. 198° is formed as a by-product. This compound forms when benzaldehyde and benzaldehyde cyanohydrin react in alcoholic solution in the presence of hydrogen chloride[69].

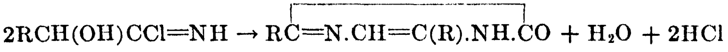
When mandelonitrile is kept for some time, it becomes viscous and a dark yellow solid deposit may form. Wood and Lilley[70] regarded this compound as an isonitrile, $C_6H_5CH(OH)N{:}C$; Baker and New[70] showed, however, that it was bis-(α-cyanobenzyloxy)-phenylmethane.

Oxazoles result from the interaction of benzaldehyde or substituted benzaldehydes with their cyanohydrins in the presence of hydrogen chloride. The mechanism of the reaction is assumed to be as follows[71]:



$$\mathrm{RCH(OH)CN} \xrightarrow{\mathrm{HCl}} \mathrm{RCH(OH)CCl{=}NH} \xrightarrow{\mathrm{R.CHO}} \mathrm{RCH(OH)CCl{=}NCH(OH)R}$$
$$\rightarrow \mathrm{RCH.CCl{=}NCH(R)O} \rightarrow \mathrm{R.C{=}CH.N{:}C(R).O}$$

Oxazole formation is favored in the absence of moisture. 3-Keto-2,5-diaryl-3,4-dihydro-1,4-diazines form through the condensation of two molecules of cyanohydrin in the presence of hydrogen chloride[67,72,73]:



$$\mathrm{2RCH(OH)CCl{=}NH} \rightarrow \mathrm{RC{=}N.CH{=}C(R).NH.CO} + \mathrm{H_2O} + \mathrm{2HCl}$$

Mandelonitrile condenses with phenols at 100° in the presence of 73% sulfuric acid to phenylhydroxyphenylacetonitriles:

$$C_6H_5CH(OH)CN + C_6H_5OH \rightarrow C_6H_5CH(CN).C_6H_4OH\ (p) + H_2O$$

Condensation also takes place with substituted mandelonitriles and the yields are generally high[74].

Reaction with Miscellaneous Carbonyl Compounds

Benzil reacts with "nascent" hydrocyanic acid to form benzil dicyanohydrin[75], $C_6H_5C(OH)(CN).C(OH)(CN).C_6H_5$.

Phenylacetaldehyde cyanohydrin, $C_6H_5CH_2CH(OH)CN$, has been prepared from *phenylacetaldehyde* and hydrocyanic acid, using pyridine as a catalyst[76]. The dinitrile of phenylmalic acid, $C_6H_5CH(CN).CH(OH)(CN)$, has been similarly obtained from *phenylcyanoacetaldehyde*[77]. Pheny-α-hydroxycrotonic nitrile, $C_6H_5CH{:}CH.CH(OH).CN$, has also been prepared by this method from *cinnamic aldehyde*[78].

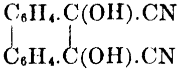
α-Hydroxy-β-*p*-anisylbutyronitrile, $CH_3OC_6H_4.COCH(CH_3)CH(OH)CN$, has been prepared from the bisulfite compound of α-*p*-anisoylpropionaldehyde and potassium cyanide. Cold concentrated hydrochloric acid converts the nitrile to the amide, m.p. 91–92°[80].

Phenyl-α-hydroxycrotonic nitrile has been prepared from the bisulfite compound of *cinnamic aldehyde* and potassium cyanide. The bisulfite compound is prepared in almost theoretical yield by adding the theoretically required quantity of alkali bisulfite to the cooled ether solution of the aldehyde. By proceeding in this manner, the formation of sulfonated compounds, resulting from the addition of the bisulfite group on the double bond, is avoided[81]. Hexahydromandelonitrile has been prepared from the bisulfite compound of hexahydrobenzaldehyde and KCN[82].

Acetophenone cyanohydrin has been obtained in poor yield by placing a concentrated ether solution of *acetophenone* in contact with an aqueous solution of potassium cyanide and passing a current of hydrogen chloride through the liquid[146].

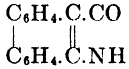
2-Methoxy-1-naphthaldehyde cyanohydrin has been prepared from the bisulfite compound of the aldehyde and alkali cyanide[76].

Phenanthraquinone dihydrocyanide,



$$\begin{array}{l} C_6H_4.C(OH).CN \\ \vert \qquad\ \ \vert \\ C_6H_4.C(OH).CN \end{array}$$

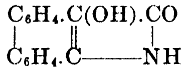
has been prepared from *phenanthraquinone* by reaction with 30% aqueous hydrocyanic acid. A stronger solution of hydrocyanic acid is without rapid action in the cold, but reacts at the temperature of boiling water bath to form a stereoisomeric dihydrocyanide. The latter is best prepared by the action of anhydrous hydrocyanic acid on phenanthraquinone in the warm[84]. The dihydrocyanide is hydrolyzed to phenanthranil,



$$\begin{array}{l} C_6H_4.C.CO \\ \vert \qquad\ \Vert \\ C_6H_4.C.NH \end{array}$$

(m.p. 241°)

and hydroxydihydrophenanthranil,



$$\begin{array}{l} C_6H_4.C(OH).CO \\ \vert \qquad\ \Vert \qquad\quad \vert \\ C_6H_4.C\text{———}NH \end{array}$$

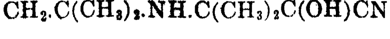
(m.p. 183°)

Cyclohexanone cyanonhydrin has been prepared from *cyclohexanone*[85]. The cyanohydrin is converted to 1-cyanocyclohexene, $b.p._{15}$ 86°, by the action of thionyl chloride[86]. The cyanohydrin of *p-methylcyclohexanone* has been prepared from the bisulfite compound of *p*-methylcyclohexanone and potassium cyanide. The nitrile is converted to the corresponding acid by heating with hydrochloric acid at 100°. The cyanohydrins of 1-methylcyclohexanone-2 and 1,3-dimethylcyclohexanone have also been prepared[87]. 1,3-Dimethylcyclohexanone-5 adds hydrocyanic acid fo form 1,3-dimethylcyclohexanone-5-nitrile(1)[88]. Ethyl 2-hydroxy-2-cyano-1:3-dimethylcyclohexane-1-carboxylate has been synthesized from ethyl 2:6-dimethylcyclohexanone-2-carboxylate in 65% yield. The nitrile could not be hydrolyzed to the corresponding acid[89].

Tetramethyl-γ-hydroxypiperidin carboxylic acid nitrile has been made from triacetonin. α-Eucain may be obtained from the nitrile by saponification to acid, followed by benzoylation. Triacetonin may be prepared by the condensation of acetone with ammonia[90].

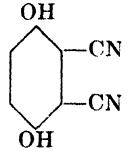
Cyclopentanone cyanohydrin has been prepared from *cyclopentanone*[91]. 2-Methylcyclopentanone cyanohydrin, $b.p._{14} = 118°$, has been similarly prepared. In the presence of pyridine thionyl chloride abstracts the elements of water from the cyanohydrin, at 100°, to form 2-methyl-Δ'-cyclopentene-1-nitrile[92].

Tetramethyl-β-pyrrolidone hydrochloride reacts with potassium cyanide to form the corresponding cyanohydrin[93],



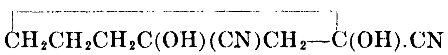
$$\overline{CH_2.C(CH_3)_2.NH.C(CH_3)_2C}(OH)CN$$

2,3-Dicyanodihydroquinone,



has been obtained from *quinone* and nascent hydrocyanic acid. Hydroquinone is formed simultaneously[94]. From the methyl ester of quinonecarboxylic acid, 3,6-dihydroxy-2-cyanomethyl benzoate is obtained[95]. 2,3-Dicyanohydroquinone is also obtained by treating monochloroquinone with hydrocyanic acid; it is oxidized by cold nitric acid to dicyanoquinone, orange prisms, m.p. 175–180°. Dicyanoquinone treated with cold hydrochloric acid gives monochlorodicyanohydroquinone[148].

Dihydroresorcinol combines with two equivalents of hydrocyanic acid to form dihydroresorcinol dicyanohydrin,



$$\overbrace{CH_2CH_2CH_2C(OH)(CN)CH_2—C}(OH).CN$$

the cyanohydrin has been hydrolized to dihydroxyhexahydro*iso*phthalimide, and the corresponding acid[152].

The cyanohydrin of *camphor* does not form directly by the union of hydrocyanic acid and camphor. The compound has been prepared from camphorimine and hydrocyanic acid, the amino nitrile, which first forms, being converted to the cyanohydrin with nitrous acid in aqueous solution. Camphor cyanohydrin is a crystalline, stable compound. The hydroxyl group in this compound is readily replaced with chlorine on treatment with aqueous hydrochloric acid. Aminonitriles are formed by the action of hydrocyanic acid on *fenchimine* and *menthimine*[96]. Cyanofenchylamine and cyanomenthylamine do not yield the corresponding cyanohydrins by treatment with nitrous acid, but form the nitriles of fenchenecarboxylic acid and menthenecarboxylic acid, respectively.

Menthon cyanohydrin has been prepared from *menthonnitramine* by reaction with potassium cyanide solution. On hydrolysis with alkalies, menthon cyanohydrin gives an unsaturated acid by loss of the elements of water; camphor cyanohydrin behaves similarly[96]. Hydrolysis with hydrochloric acid yields a lactone, $C_{10}H_8.CO_2$, m.p. 78–79°.

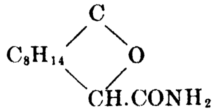
Cyanohydrins have been made from *pernitrosofenchon* and *pernitrosocamphor* by reaction with potassium cyanide and subsequent hydrolysis with a mineral acid[97].

d-5-Oxocamphor cyanohydrin has been prepared directly from hydrocyanic acid and *d-5-oxocamphor*[98].

Lapworth[99] prepared camphorquinone cyanohydrin from *camphorquinone* and hydrocyanic acid. He observed that the presence of small quantities of acid caused retardation of the reaction, and the addition of basic compounds, including ammonia or organic bases, caused a marked acceleration. The catalytic effect appeared to be in proportion to the strength of the base employed.

Dehydroandrosteron acetate has been converted to the corresponding cyanohydrin by the action of hydrocyanic acid; the cyanohydrin has been dehydrated to the 16,17-dehydronitrile, and from this desoxycorticosteron has been synthesized, a compound which has acquired great clinical importance[100].

The bisulfite compounds of esters of β-camphoraldehydecarboxylic acid react with potassium cyanide to form the corresponding cyanohydrins, $C_8H_{14}(COOR).CH(OH)CN$. Concentrated sulfuric acid transforms these compounds into β-carboxamide-β-campholide[101],



REACTION OF ALKALI CYANIDES WITH ALDEHYDES AND KETONES

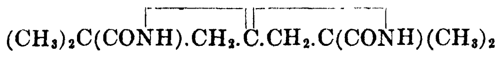
Reaction with Aldehydes

Since alkali cyanides are slightly dissociated in aqueous solution to hydrocyanic acid and the hydroxide of the alkali metal, it is to be expected that a certain amount of cyanohydrin will form when aldehydes or ketones are added to solutions of alkali cyanides. Appreciable quantities of cyanohydrin may form at higher temperatures, but at these temperatures, other reactions also take place simultaneously. Wislicenus[102] reported the formation of γ-cyano-*n*-potassium valerate from γ-*n*-valeracetone and aqueous potassium cyanide at 280–290°

Potassium cyanide in aqueous solution reacts with *formaldehyde* to form a variety of products: glycolic acid, the secondary aminoacid, $HN(CH_2COOH)_2$, and the tertiary aminoacid, $N(CH_2COOH)_3$. Polstorff and Meyer[103] assume that $KOCH_2CN$ is first formed. The reaction of potassium cyanide with formaldehyde in alkaline solution is quantitative and forms the basis for a method of determination of formaldehyde[104].

Potassium cyanide causes the condensation of *acetaldehyde* to aldol[107]. In concentrated aqueous solution, potassium cyanide reacts with acetaldehyde at 225–235° forming alanine and α,α′-iminodipropionic acid[105]. Hydracetylacetone, $CH_3CH(OH).CH_2.CO.CH_3$, forms through the condensation of acetone in the presence of potassium cyanide[107]. Aqueous potassium cyanide converts *isobutyraldehyde* to isobutyraldol cyanohydrin[106].

Mesityl oxide reacts in aqueous solution with potassium cyanide to form mesitonitrile, $(CH_3)_2C(CN).CH_2.COCH_3$, and mesitonitrile cyanohydrin[108], $(CH_3)_2.C(CN).CH_2.C(OH)(CN).CH_3$. *Phorone* reacts with potassium cyanide in hot alcoholic solution to form phorone dinitrile[109], $(CH_3)_2.C(CN).CH_2.CO.CH_2.C(CN)(CH_3)_2$. Anschütz[110] believes the compound is an internal diamide anhydride,



$$(CH_3)_2C(CONH).CH_2.C.CH_2.C(CONH)(CH_3)_2$$

Phenylacetaldehyde, reacting with potassium cyanide in alcoholic solution. gives α,γ-diphenyl-β-hydroxybutyraldehyde cyanohydrin, $C_6H_5CH_2CH(OH).CH(C_6H_5).CH(OH)CN$, m.p. 144–146°; on hydrolysis, this is transformed to α-hydroxy-β-phenyl-γ-benzylbutyrolactone[151].

Reaction with Chloral and Crotonchloral

Chloral reacts with potassium cyanide in aqueous solution to form dichloroacetic acid[111],

$$Cl_3C.CHO + KCN + H_2O \rightarrow Cl_2.CH.COOH + KCl + HCN$$

Pinner believed that the reaction involved the following steps:

$$Cl_3C.CHO + KCN + H_2O \rightarrow Cl_3C.CH(OH)CN + KOH$$
$$Cl_3CCH(OH)CN \rightarrow Cl_2C{:}COH.CN \rightarrow Cl_2CHCO.CN$$
$$Cl_2CHCOCN + 2KOH \rightarrow Cl_2CH.COOK + KCN + H_2O$$

According to Kötz, the steps involved are the following:

$$Cl_3C.CHO + HCN \rightarrow Cl_3CCH(OH)CN$$
$$\xrightarrow{(-HCl)} Cl_2CH.CO.CN \xrightarrow{(+H_2O)} Cl_2CH.COOH + HCN$$

There is also formed some chloral cyanohydrin, which condenses with unconverted chloral to give 6-keto-2,4,7-tri-(trichloromethyl)-1,3,5-dioxazseptan

$$Cl_3C\overline{CH.O.CH(CCl_3).O.CH(CCl_3).NH.CO}$$ [m.p. 123 (dec.)]

In the absence of diluents, the reaction is violent. If the reaction is carried out in alcoholic solution, one of the products of the reaction is the methyl ester of dichloroacetic acid, chloral cyanohydrin and potassium dichloroacetate forming at the same time.

Crotonchloral, $Cl_3C.CH{:}CH.CHO$, reacts with an alcoholic solution of potassium cyanide to form monochlorocrotonic acid ethyl ester[112], $ClCH_2.CH{:}CH.COOC_2H_5$.

REACTION OF ALKALINE EARTH CYANIDES WITH ALDEHYDES AND KETONES

Aldehydes and ketones react with calcium and other alkaline earth cyanide to form solid compounds, some of which are of the type, $R_1R_2C(CN).O.A.OC(CN)R_1R_2$, "A" representing an atom of the alkaline earth metal[113].

SOME REACTIONS OF CYANOHYDRINS

Replacement of the Hydroxyl Group in Cyanohydrins with Chlorine

The hydroxyl group in glycolic nitrile may be replaced with chlorine by the action of thionyl chloride in the presence of organic bases such as pyridine, dimethylaniline, etc. According to Gerard[118], the reaction proceeds in three steps:

$$HOCH_2CN + SOCl_2 + 2R_3N \rightarrow SO(OCH_2CN)_2 + 2R_3N.HCl$$
$$SO(OCH_2CN)_2 + SOCl_2 \rightarrow 2CNCH_2OSOCl \rightarrow 2CNCH_2Cl + 2SO_2$$

The hydroxyl group in ethylene cyanohydrin may be similarly replaced with chlorine by the action of thionyl chloride[119].

Methoxyphenylchloroacetonitrile, b.p.$_{13}$ 153–155°, has been made by the action of thionyl chloride on anisaldehyde cyanohydrin in the cold. *p,p′*-Dimethoxydiphenylmalononitrile forms simultaneously[120]. 2-Methoxy-1-naphthylchloroacetonitrile has also been prepared in 50% yield by the action of thionyl chloride on 2-methoxynaphthaldehyde cyanohydrin in benzene solution at the boiling temperature of benzene. At a low temperature di-2-methoxy-1-naphthylcyanomethyl ether (m.p. 121°) is formed. This compound may also be converted to 2-methoxy-1-naphthylchloroacetonitrile by treatment with excess thionyl chloride in boiling benzene solution. A chloronitrile has been obtained from cinnamaldehyde cyanohydrin and thionyl chloride, but this compound was found to be unstable and deposited a chlorine-free white, crystalline compound melting at 114°, which is probably 2,5-diphenyldihydroterephthalonitrile[120].

Mandelonitrile has been converted to phenylchloroacetonitrile, b.p.$_{13}$ 131.5° by reaction with phosphorus oxychloride[121],

$$3C_6H_5\,CH(OH)CN + POCl_3 \rightarrow 3C_6H_5CHCl.CN + H_3PO_4$$

This compound may be condensed with sodium ethoxide to dicyanostilbene, m.p. 158°:

$$2C_6H_5CHCl.CN + 2NaOC_2H_5 \rightarrow C_6H_5C(CN){:}C(CN).C_6H_5 + 2NaCl + 2C_2H_5OH$$

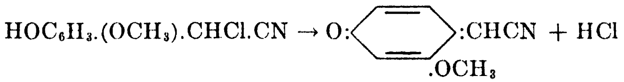
Phenylchloroacetonitrile reacts with nitrosobenzene in presence of alkali to form two isomeric *N*-phenyl ethers of oximinophenylacetonitrile[122]:

$$C_6H_5CHCl.CN + ON.C_6H_5 \rightarrow C_6H_5C(CN){:}NO.C_6H_5 + HCl$$

The hydroxyl group in vanillin cyanohydrin may be replaced with chlorine by the action of phosphorus trichloride, or phosphorus pentachloride:

$$3HOC_6H_3(OCH_3).CH(OH)CN + PCl_3 \rightarrow 3HOC_6H_3(OCH_3).CHCl.CN + H_3PO_3$$

The compound is unstable and changes to 3-methoxyquinocyanomethid in aqueous solution:



Heated with hydrogen iodide for a short period, it forms 3,3′-dimethoxy-4,4′-dihydroxy-α′α-dicyanostilbene,[123] $HOC_6H_3(OCH_3).CH(CN)CH(CN).C_6H_3(OCH_3)$-OH.

The hydroxyl group in other cyanohydrins has been replaced by chlorine by use of phosphorus pentachloride[124]. The OH-group in phenylacetaldehyde cyanohydrin has been replaced with chlorine by the action of phosphorus pentachloride in benzene, to form α-chloro-β-phenylpropionitrile, b.p.$_{13}$ 128–130°, in 62% yield[120]. α-Chloro*iso*butyronitrile is formed when acetone cyanohydrin is treated in benzene solution with phosphorus pentachloride at 25–30°. Under the same conditions, phosphorus trichloride forms the tri-α-cyano*iso*propyl ester of meta-phosphoric acid[125]:

$$3(CH_3)_2C(CN)OH + PCl_3 \rightarrow [(CH_3)_2C(CN)O]_3P + 3HCl$$

Concentrated hydrochloric acid reacting in a sealed tube with ethylene cyanohydrin forms β-chloropropionic acid; hydrogen bromide gives β-bromopropionic acid[153].

Hydrogen chloride reacts with mandelonitrile or substituted mandelonitriles to form α-chloro amides. These may be reduced catalytically to substituted acetamides[126].

Certain α-chloronitriles form quaternary amino compounds with pyridine. Quaternary compounds have been obtained, for example, from chloroacetonitrile, chloropropionitrile, phenylchloroacetonitrile, α-chloro-β-phenylpropionitrile and *p*-methoxyphenylchloroacetonitrile[120].

Acylation of Cyanohydrins: Other Reactions

The hydroxyl group in cyanohydrins may be replaced by acid residues. Thus, acetylcyanohydrins may be prepared by the action of acetic anhydride on cyanohydrins in the presence of a small quantity of sulfuric acid:

$$R.CH(OH)CN + O(COCH_3)_2 \rightarrow RCH(CN).OCOCH_3 + HOCOCH_3$$

Pyrolytic decomposition of acetylcyanohydrins results in the formation of unsaturated nitriles. Thus, vinyl cyanide results from the pyrolytic decomposition of α-acetoxypropionitrile:

$$CH_3CH(CN).OCOCH_3 \rightarrow CH_2{:}CH.CN + HOCOCH_3$$

Similarly, methacrylic nitrile results from the pyrolysis of α-acetoxyisobutyronitrile. The pyrolysis takes place best at 490°.

Phenylacetoxyacetonitrile has been prepared by the action of acetic anhydride on mandelonitrile. α-Acetoxy nitriles may also be prepared from cyanohydrins and acetyl chloride:

$$RCH(CN)OH + Cl.CO.CH_3 \rightarrow RCH(CN)O.CO.CH_3 + HCl$$

Cy this reaction, Colson[127] prepared α-acetoxypropionitrile, $CH_3CH(CN)O.CO.BH_3$, b.p. 169°; α-acetoxybutyronitrile, $CH_3CH_2C(CN)OCOCH_3$, b.p. 183°; and α-propionoxybutyronitrile, $CH_3CH_2.CH(CN)OCO.C_2H_5$, b.p. 181°. Similarly, glycinonitrile has been acylated by reaction with acyl chlorides to cyanomethyl esters of carboxylic acids[83]. α-Benzoyloxypropionitrile has been prepared in a similar way from aldehyde cyanohydrin and benzoyl chloride[128]:

$$CH_3CH(CN)OH + ClCO.C_6H_5 \rightarrow CH_3CH(CN)OCOC_6H_5 + HCl$$

Benzoylated aromatic cyanohydrins, $ArCH(OCOC_6H_5)CN$, have been reduced by means of tetralin to arylacetonitriles[149], $ArCH_2CN$.

α-Acetoxy cyanohydrins have also been obtained through the interaction of cyanohydrins with vinyl acetate and with acetic acid in the presence of catalytic quantities of *p*-toluenesulfonic acid[157].

Verhulst[131] showed that concentrated sulfuric acid gives sulfoamides with cyanohydrins; thus, the compound, $RCH(OSO_3H).CO.NH_2$, has been obtained from acetaldehyde cyanohydrin. In some cases, sulfoacids are formed from which neutral salts of the type $RCH(OSO_3Na).COONa$, have been isolated.

Mandelonitriles have been condensed with benzene, toluene, etc., by heating the cyanohydrin with an excess of the hydrocarbon in the presence of stannic chloride:

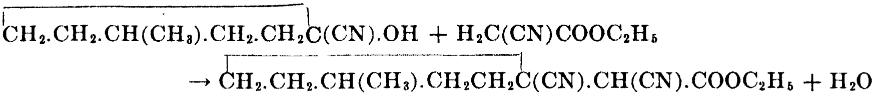
$$C_6H_5CH(CN).OH + C_6H_6 \rightarrow (C_6H_5)_2CH.CN + H_2O$$

The yields of diaryl acetonitrile were with toluene 30 %, with mesitylene 40 %, with naphthalene 40–45 %[132].

Mandelonitrile reacts with benzyl cyanide in the presence of potassium cyanide to form diphenylsuccinonitrile:

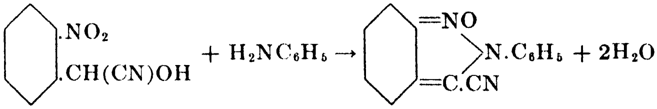
$$C_6H_5CH_2CN + C_6H_5\,CH(OH).CN \rightarrow C_6H_5CH(CN).CH(CN).C_6H_5 + H_2O$$

Ethyl cyanoacetate has been condensed with 4-methylcyclohexanone cyanohydrin in the presence of sodium ethoxide to ethyl-l-cyano-4-methylcyclohexane-l-cyanoacetate[133]:



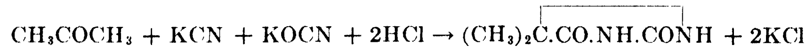
$$CH_2.CH_2.CH(CH_3).CH_2.CH_2C(CN).OH + H_2C(CN)COOC_2H_5 \rightarrow CH_2.CH_2.CH(CH_3).CH_2CH_2C(CN).CH(CN).COOC_2H_5 + H_2O$$

o-Nitromandelonitrile condenses with aniline to 2-phenyl-3-cyanoindazole-N-oxide:



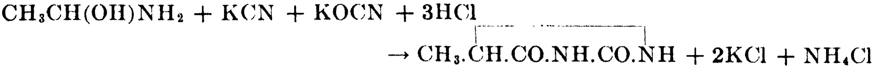
m-Nitromandelonitrile reacts in normal manner forming the phenylaminonitrile, $NO_2C_6H_4.CH(CN).NH.C_6H_5$, which exists in two modifications, one colorless the other yellow[134].

Acetonylurea forms when hydrocyanic acid is added to a mixture of acetone, potassium cyanide and potassium cyanate[135]:



$$CH_3COCH_3 + KCN + KOCN + 2HCl \rightarrow (CH_3)_2C.CO.NH.CONH + 2KCl$$

Lactylures forms when an aqueous solution containing aldehyde ammonia, potassium cyanide and potassium cyanate is made strongly acid,



$$CH_3CH(OH)NH_2 + KCN + KOCN + 3HCl \rightarrow CH_3.CH.CO.NH.CO.NH + 2KCl + NH_4Cl$$

Urech obtained this compound through the interaction of alanine and cyanic acid[136].

Acylated cyanohydrins may be converted to amides by boiling with zinc oxide in glacial acetic acid. Albert proceeded as follows:

> Two grams of the acyl cyanohydrin were dissolved in 10 cc of glacial acetic acid. One gram of zinc oxide was added and the liquid heated to boiling; 2 cc of water were then added gradually in the course of a quarter to one-half hour, when all of the zinc oxide went into solution. The amide was then recovered.

The yields are generally above 80%[155].

Acylated Cyanides Directly from Aldehydes and Acyl Chlorides

Aldehydes and ketones react with alkali cyanides in aqueous or aqueous-alcoholic solution in the presence of benzoyl chloride, forming benzoylated cyanohydrins:

$$RR'CO + KCN + ClCO.C_6H_5 \rightarrow RR'C(CN)OCO.C_6H_5 + KCl$$

Aloy and Rabaut[114] have prepared a large number of benzoylated nitriles by this reaction. Among the compounds prepared by these authors are the benzoylated cyanohydrins of *p*-benzoxyacetaldehyde, formaldehyde, acetaldehyde, furfuraldehyde[115]; acetone, methylethyl ketone, diethyl ketone, cyclohexanone[116]; cyanohydrins of cinnamic- and cuminic aldehydes, cyclopentanone, and glyoxal[117]. The method does not work successfully with aliphatic acyl chlorides[129].

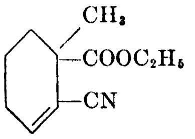
Cyanomethyl methacrylate, crotonate, β-chlorocrotonate, cinnamate and α-methylcinnamate have been obtained in good yield through the interaction of the chlorides of the corresponding acids with formaldehyde and sodium cyanide in aqueous solution. Cyanomethyl acrylate has been obtained in low yield by this method[130].

Dehydration of Cyanohydrins

Certain cyanohydrins have been successfully dehydrated by heating under reflux a mixture of equivalent quantities of the cyanohydrin and *thionyl chloride*. The following unsaturated nitriles were prepared in 70 to 75% yield by this method[137]:

α-Ethyl-β-methylacrylonitrile	from diethyl ketone cyanohydrin
α-Methyl-β-ethylacrylonitrile	from methyl propyl ketone cyanohydrin
α-Propyl-β-ethylacrylonitrile	from dipropyl ketone cyanohydrin
α-*Iso*propyl-β, β-dimethylacrylonitrile	from *iso*butyrone cyanohydrin

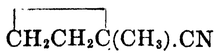
2-Carbethoxy-2-methylcyclohexanone cyanohydrin has been dehydrated with thionyl chloride and pyridine to l-carbethoxy-2-cyano-l-methyl-Δ^2-cyclohexene,



Tetrahydro-*o*-tolunitrile, b.p.$_{10}$ = 85–86°, has been similarly prepared from 2-methylcyclohexanone cyanohydrin, b.p.$_{10}$ = 122–123°[150].

Cyanohydrins, in general, may be dehydrated with phosphorus pentoxide. Thus acetone cyanohydrin is readily dehydrated by this compound at 10–15° to α-methylacrylonitrile[138], $CH_2{:}C(CH_3).CN$.

1-methylcyclopropyl cyanide,



$$\overline{CH_2CH_2C}(CH_3).CN$$

has been made from α-methylacrylonitrile by condensation with cyanamide followed by decomposition of the resulting pyrazolin by heat[139].

Acid sulfuric esters have been proposed as dehydrating agents for cyanohydrins; unsaturated esters are stated to be the final product of the reaction[140].

Unsaturated amides are formed when ketone cyanohydrins are heated for a short time at 140–180° with concentrated sulfuric acid, or oleum, or aminoalkyl esters of sulfuric acid in the presence of inhibitors of polymerization such as copper powder[141].

Ethylene cyanohydrin and homologous β-hydroxynitriles may be dehydrated by passing the vapors of the cyanohydrin over a dehydrating catalyst at elevated temperature.

Unsaturated nitriles are obtained by the pyrolytic decomposition of acetylated cyanohydrins. Thus, acrylonitrile results from the pyrolysis of α-acetoxypropionitrile:

$$CH_3.CH(OCO.CH_3).CN \rightarrow CH_2{:}CHCN + HOCOCH_3$$

Similarly, methacrylic nitrile forms from α-acetoxyisobutyronitrile. Methacrylic nitrile also results from the pyrolysis of N-acetyl-α-acetoxyisobutyramide at 515–530°. β-Acetoxypropionitrile also yields acrylonitrile on pyrolysis at 350–370°[142]. 1-Cyano-1,3-butadiene has been obtained by the pyrolysis at 470° of an ester of crotonaldehyde cyanohydrin[143]:

$$CH_3CH{:}CH.CH(CN).OCOCH_3 \rightarrow CH_2{:}CH.CH{:}CH.CN + HOCOCH_3$$

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Chapter 10

Aminonitriles Derived from Aldehydes and Ketones

Alpha-aminonitriles may be prepared:

(1) By the direct replacement of the hydroxy group in aldehyde or ketone cyanohydrins by reaction with ammonia or amines.

(2) By the reaction of ammonium cyanide or amine cyanides with aldehydes or ketones.

(3) By the reaction of hydrocyanic acid with the amino compound of aldehydes or ketones.

The reaction between cyanohydrins and ammonia is reversible and does not, therefore, proceed to completion unless one of the products of the reaction, the water for example, is eliminated from the sphere of reaction. A large excess of ammonia, and the presence of compounds that have a strong affinity for water and do not otherwise interfere with the reaction, favor the formation of aminonitrile. β-Aminonitriles are not formed by the direct action of amines on β-hydroxy nitriles[1].

Aminonitriles from Aliphatic Cyanohydrins

Aminoacetonitrile may be prepared from formaldehyde cyanohydrin and ammonia. Menge[2] prepared aminoacetonitrile by dissolving formaldehyde cyanohydrin in liquid ammonia, sealing the container and allowing the solution to stand at room temperature for 24 hours, then evaporating off the excess of ammonia. The yield of aminonitrile was 95% of theory. The preparation of aminonitriles, by the reaction of hydroxy nitriles with liquid ammonia or supersaturated solutions of ammonia in a closed vessel, is protected by *British patent* 436,692 (1935).

The nitrile may be hydrolyzed with aqueous hydrochloric acid to aminoacetic acid. The acid condenses with formaldehyde to form methyleneiminoacetic acid, $CH_2{=}N.CH_2COOH$. The esters of aminoacetic acid condense in aqueous solution to 2,5-dioxypiperazine,

$$\overline{\mathrm{CO.CH_2.NH.CO.CH_2NH}}$$

Curtius[3] prepared diazoacetonitrile, N_2CHCN, by the reaction of nitrous acid with glycinonitrile hydrochloride at a low temperature. The reaction proceeds slowly and requires several days for completion. Diazoacetonitrile is an orange-yellow, mobile liquid readily soluble in water; it has a pleasant odor when freshly made. The vapors attack the mucous membrane. The compound is very unstable, and *explodes violently* in contact with copper oxide.

Aminoacetonitrile heated with phthalic anhydride forms phthaliminoacetonitrile, $C_6H_4(CO)_2NCH_2CN$, plates melting at 123–124°. 4-Chloro-, 3-nitro-, 4-nitro-, 3,6-

dichloro-, 3,6-dibromo- and tetrachlorophthaliminoacetonitriles have also been made in the same manner[87].

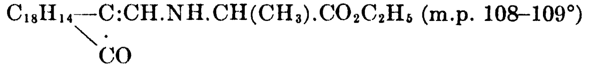
Diethylaminoacetonitrile is obtained by heating a mixture of formaldehyde cyanohydrin and diethylamine on a water-bath for 6 hours.

N-(Cyanomethyl)-glycine ethyl ester, $CNCH_2NHCH_2COOC_2H_5$, has been obtained by the reaction of glycine ethyl ester with a mixture of potassium cyanide and the bisulfite compound of formaldehyde. N-(cyanomethyl)-alanine, ethyl N-(α'-cyanobenzyl)-β-aminobutyrate and diethyl N-(cyanomethyl)-α,α'-iminodipropionate have been made by the same method[88].

Methylaniline, heated for ten hours at 100° with a solution of formaldehyde cyanohydrin in absolute alcohol, forms *N-methylphenylaminoacetonitrile,* $C_6H_5N(CH_3)CH_2CN$, a colorless liquid boiling at 266°[89].

Alanine nitrile, $CH_3CH(NH_2).CN$, may be prepared in a similar manner from acetaldehyde cyanohydrin and ammonia. The reaction product is a mixture of *d*- and *l*-nitriles which may be converted to *d*-and *l*-alanine[4].

l-Alanine may be separated from the mixture by conversion to *d*-methylenecamphor-*l*-alanine ethyl ester,



$$C_{18}H_{14}\!\underset{\diagdown\!\overset{\cdot}{C}O}{—}C{:}CH.NH.CH(CH_3).CO_2C_2H_5 \text{ (m.p. 108–109°)}$$

by reaction with *d*-hydroxymethylenecamphor. The compound is then hydrolyzed with hydrochloric acid, and the free hydroxymethylenecamphor is distilled by steam.

α-Dimethylamino- and *α-piperidinopropionitriles* have been prepared by Klages[5], and α-anilido-, α-*p*-toluido-, α-*o*-toluidopropionitriles by Tiemann and Stephan[6] from acetaldehyde cyanohydrin and the appropriate amines.

Methyl-α-cyanoethylaniline, $C_6H_5N(CH_3).CH(CN)CH_3$, b.p. 212° (dec.), has been prepared in 65% yield from methylaniline and acetaldehyde cyanohydrin; *p-nitroso methyl-α-cyanoethylaniline,* m.p. 75.5° has been obtained similarly in 95% yield. This latter has been condensed with *p*-nitrobenzyl cyanide to $NO_2.C_6H_4.C(CN){:}NC_6H_4N(CH_3).CH(CN)CH_3$. Similar condensation products have also been prepared from benzyl cyanide and from *p*-nitrobenzyl cyanide and the amide obtained by the partial hydrolysis of *p*-nitrosomethyl-α-cyanoethylaniline. The amide has also been condensed with malononitrile to[7] $(CN)_2C{:}N.C_6H_4.N(CH_3).CH(CONH_2).CH_3$.

Chloroacetaldehyde cyanohydrin reacts with dimethylamine to form α-dimethylaminoacrylonitrile[8],

$$ClCH_2CH(OH)CN + HN(CH_3)_2 \rightarrow CH_2{=}C(CN).N(CH_3)_2.HCl$$

α-Aminoisobutyronitrile has been prepared in 85% yield by saturating acetone cyanohydrin with gaseous ammonia and adding anhydrous sodium sulfate[9].

Substituted α-amino*iso*butyronitriles have also been prepared through the interaction of acetone cyanohydrin with the following amines: dimethylamine, diethylamine, ethanolamine, dicyclohexylamine, ethylenediamine, aniline, *p*-aminophenol, piperidine[9]. α-Amino*iso*butyronitrile has been converted to 5,5-dimethyl-2,4-dithiohydantoin by reaction with carbon bisulfide.

The amination of cyanohydrins can proceed in the direction of the formation of secondary and tertiary amino compounds[90]:

$$RCH(CN)NH_2 + HOCH(CN)R \rightarrow RCH(CN).NH.CH(CN)R + H_2O$$
$$RCH(CN).NH.CH(CN)R + HOCH(CN)R \rightarrow (RCH(CN))_3N + H_2O$$

α-Amino*iso*butyronitrile gradually changes to α-iminodi*iso*butyronitrile on standing at room temperature. This tendency to form an iminonitrile is shown also by α-amino-*iso*butylacetonitrile and amino-1-cyclohexanone nitrile[91]. α-Hydroxypropionitrile, reacting with the nitrile ester of *sym.*-diphenyliminodiacetic acid, replaces the phenylacetonitrile group forming the compound[92] $C_2H_5OCO.CH(C_6H_5)NH.CH(CH_3)CN$.

Diacetyl- and acetylpropionyl cyanohydrins, $CH_3C(OH)(CN).C(OH)(CN).CH_3$, and $CH_3.C(OH)(CN).C(OH)(CN)C_2H_5$, have been converted to the corresponding aminonitriles by treatment with ammonia. These compounds are converted to $C_6H_8N_3Cl$, and $C_7H_{10}N_3Cl$ (m.p. 77.5°), respectively, on treatment with hydrochloric acid[10].

Cyclohexanone cyanohydrin reacts readily with phenylhydrazine to form a crystalline compound of symmetrical structure[107].

Chloral cyanohydrin reacts with urea to form trichloroethylidene diureid[11], $Cl_3C.CH(NHCONH_2)_2$.

Aminonitriles from Aromatic Cyanohydrins

Aminophenylacetonitrile is obtained by allowing a solution of mandelonitrile in an equivalent quantity of concentrated ammonium hydroxide to stand for six hours. Concentrated hydrochloric acid converts the nitrile to aminophenylacetamide hydrochloride. The amide decomposes on heating to benzylammonium benzylcarbamate, $C_6H_5CH_2NH.CO.OH.H_2NCH.C_6H_5$ and benzylamine.

Benzaldehyde cyanohydrin reacts with ammonia in alcoholic solution in the presence of potassium hydroxide to form α-amino-α-phenylacetamide[12], C_6H_5-$CH(NH_2).CONH_2$. Phenylsarcosine nitrile, $C_6H_5CH(NHCH_3).CN$, has been obtained from mandelonitrile and methylamine[13]. With aniline and in the presence of a small quantity of potassium cyanide, phenylanilinoacetonitrile (m.p. 85°) forms. The reaction is best carried out by mixing equivalent quantities of benzaldehyde cyanohydrin and aniline with a small amount of potassium cyanide, allowing the mixture to stand twelve hours at room temperature, then heating at 50–60° for a short time[14].

A condensation product has been prepared from α-anilinophenylacetonitrile and acetophenone; Clarke and Lapworth[51] believed this to be γ-cyano-α-benzoyl-γ-anilino-β,γ-diphenylpropane, while Bodforss[48] considered it more probable that it is 1,2,3,5-tetraphenyl-2-cyano-5-hydroxytetrahydropyrrole.

Aldehydes react with anilinophenylacetonitrile, and other substituted aminonitriles, forming methyleneimides[52],

$$C_6H_5CH(CN).NH.C_6H_5 + OCH.C_6H_5 \rightarrow C_6H_5CH.(NHC_6H_5).CO.N{:}CHC_6H_5$$

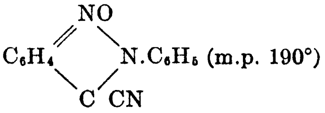
Knoevenagel[14] prepared *p*-toluidinophenylacetonitrile, $C_6H_5CH(CN).NH.$-$C_6H_4CH_3$, m.p. 109°, and α-naphthylaminophenylacetonitrile, m.p. 106°.

Phenyl-*m*-toluidino-, -*m*-chloranilido-, and -α-dibromanilido-acetonitriles have been prepared from mandelonitrile and the appropriate amines[15]. *p*-Chloraniline gives with mandelonitrile the compound, $C_{35}H_{24}O_3N_2Cl_2$, the structure of which is not known; *o*-toluidine does not react with mandelonitrile.

Bucherer and Grolée[16] prepared the following substituted phenylaminoacetonitriles in the yields indicated:

	M.P. °*C*	*Yield* %
o-Toluidinophenylacetonitrile	72–73	50
p-Toluidinophenylacetonitrile	108–109	58
p-Hydroxyanilidophenylacetonitrile	175–180(dec.)	89.4
p-Methoxyanilidophenylacetonitrile	73–74	88.3
p-Aminoanilidophenylacetonitrile		
m-Aminoanilidophenylacetonitrile	90–91	83
β-Naphthylaminophenylacetonitrile	119	quantitative
Anilidophenylmethylacetonitrile	155–156	43

m-Nitrobenzaldehyde cyanohydrin condensed with aniline gives two isomeric *m*-nitrophenylanilidoacetonitriles, one yellowish red melting at 102° and the other colorless, melting at 90°. *m*-Chlorobenzaldehyde cyanohydrin has also been condensed with aniline to form the corresponding anilidoacetonitrile, melting at 83°. *o*-Nitrobenzaldehyde cyanohydrin, reacting in alcoholic solution with aniline in the presence of sodium acetate, forms 2-phenyl-3-cyanoindazole-N-oxide,



the reaction requiring two to three days for completion[93].

Benzaldehyde cyanohydrin reacts with *urea* to form *cyanobenzylurea*[17], $C_6H_5CH(CN).NHCONH_2$. Reaction proceeds in a different manner with *urethane*, *benzylidenediurethane* being formed by the elimination of one molecule of water and one of hydrocyanic acid, only half of the cyanohydrin taking part in the reaction:

$$C_6H_5CH(OH)CN + 2H_2N.CO.OC_2H_5 \rightarrow C_6H_5CH(NH.COOC_2H_5)_2 + H_2O + HCN$$

Cyanobenzylurethane, $C_6H_5CH(CN).NH.COOC_2H_5$, may be obtained in 80% yield if the reaction is carried out in the presence of one molecular equivalent of anhydrous zinc chloride[18].

Aniline reacts with *acetophenone cyanohydrin* to form *phenylanilidopropionitrile*[19], $C_6H_5C(CN)(CH_3).NHC_6H_5$.

α-Anilidoisobutyronitrile, m.p. 93–94° has been prepared from aniline and *acetone cyanohydrin*[20]. *Ethyl α-naphthyl ketone cyanohydrin* has been converted to the corresponding α-aminonitrile; from the latter, 5,5-α-naphthylethylhydantoin has been obtained by reaction with potassium cyanate and hydrochloric acid, followed by hydrolysis[21]:

$$C_{10}H_7C(C_2H_5)(CN).NH_2 + HOCN \rightarrow C_{10}H_7C(C_2H_5)(CN).NHCONH_2$$

$$\rightarrow C_{10}H_7\overline{C(C_2H_5)CO.NH.CO.NH}$$

Arylaminocyanomethylcyclohexanes have been prepared by Betts and Plant[22].

Bukhsh and co-workers[23] prepared a number of compounds of this type from 3-methyl- and 4-methylcyclohexanone cyanohydrins and aniline, *p*-bromaniline, *o*-, *m*- and *p*-toluidines, α- and β-naphthylamines. Two isomeric forms of the compounds were identified.

Desai and co-workers[24] similarly prepared 2-arylamino-2-cyano-*trans*-decahydronaphthalenes from *trans*-β-decalone and the above amines. These compounds also exist in two isomeric forms.

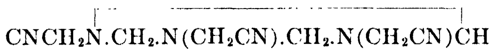
The commercial preparation of a number of aminonitriles from cyanohydrins and amines has been protected by patents[121].

Reaction of Aldehydes and Ketones with Amine Cyanides

Aminonitriles from Aliphatic Aldehydes and Ketones. Formaldehyde reacts with an aqueous solution of potassium cyanide and ammonium chloride to form methyleneiminoacetonitrile in 62% yield:

$$2CH_2O + KCN + NH_4Cl \rightarrow CH_2{=}N.CH_2.CN + KCl + H_2O$$

This compound, which melts at 129°, apparently exists only in the trimeric form[25]:



$$CNCH_2N.CH_2.N(CH_2CN).CH_2.N(CH_2CN)CH_2$$

A compound, melting at 86° is a by-product of the reaction and may be isolated from the mother liquor; according to Delépine[26] it has the structure: $(CNCH_2)_2$-$N.CH_2N(CH_2.CN)_2$. Two isomeric forms of this compound have been identified, one (α-isomer) hydrolyzed with hydrochloric acid to aminoacetic acid ethyl ester, the other (β-isomer) giving on hydrolysis ammonium chloride and a nitrogenous compound of unknown structure[94]. Hippuric nitrile $C_6H_5CO.NH.$-CH_2CN, m.p. 144°, has been obtained by the interaction of aminoacetonitrile and benzoyl chloride in 80% yield[27].

Ortho- and *para*-toluidinoacetonitriles have been made by adding aqueous formaldehyde to a mixture of *o*- or *p*-toluidine and hydrocyanic acid. α-Ortho- and para-toluidinopropionic nitriles have been prepared by the same method from *o*- or *p*-toluidine, hydrocyanic acid and acetaldehyde[95].

Acetaldehyde reacts with ammonium cyanide to form α-aminopropionitrile[28].

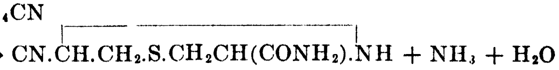
A method of preparation of substituted α-aminoacids of the aliphatic series from an aromatic amine, an aliphatic aldehyde and sodium cyanide in aqueous solution is protected by *U. S. patent* 1,933,566.

Aminonitriles may be prepared from aldehydes by shaking an etheral solution of the aldehyde with an aqueous solution of potassium cyanide and ammonium chloride[29]. Substituted aminonitriles have been prepared by adding the equivalent quantity of potassium cyanide to an aqueous solution of the amine hydrochloride, then adding the aldehyde in 30% excess. The reaction is complete in from two to forty-eight hours, depending on the aldehyde or amine used. Aminonitriles may also be prepared from ketones by this method[30].

d-Valeraldehyde reacts with ammonium cyanide to form *aminovaleronitrile;* this on saponification yields *iso*leucin and *d*-allo*iso*leucin[31]. *Iso*valeraldehyde reacts with ammonium cyanide to form the compound[28] $C_{18}H_{33}N_6$. *Ethyl-cyanoisovaleraminoacetate*, $C_4H_9.CH(CN)NHCH_2COOC_2H_5$, has been obtained by the interaction of *iso*valeraldehyde with potassium cyanide and glycine ethyl ester hydrochloride[96].

Thiodiacetaldehyde reacts with ammonium cyanide to form *3-cyanothiazan*-5-*carboxylic amide*[32],

$$OCH.CH_2.S.CH_2CHO + 2NH_4CN$$



$$\rightarrow CN.CH.CH_2.S.CH_2CH(CONH_2).NH + NH_3 + H_2O$$

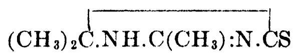
Glyoxal reacts with ammonium cyanide to form *glycolonitrile* and formamide. The former gives glycinonitrile by reaction with ammonia derived from ammonium cyanide, the over-all reaction being[33]:

$$CHO.CHO + 2NH_4CN \rightarrow HCONH_2 + NH_2.CH_2CN + HCN. + H_2O$$

Chloroaldehydes do not form aminonitriles with ammonium chloride and potassium cyanide[34].

Ammonium cyanide reacts with aliphatic and mixed aryl-aliphatic ketones to form aminonitriles[35]; ammonium cyanide does not react, however, with purely aromatic ketones[36].

Acetone reacts with ammonium cyanide to form α-amino*iso*butyronitrile[37]. The nitrile has been obtained in 80 to 85% yield by adding acetone to a concentrated aqueous solution of potassium cyanide and ammonium chloride, saturating the solution with gaseous ammonia, then heating at 50° and finally extracting the nitrile with ether[38]. Helsing converted the aminonitrile to α-acetylaminonitrile and from this, he prepared the compound,



$$(CH_3)_2C.NH.C(CH_3):N.CS$$

Gulewitsch and Wasmus[39] prepared aminonitriles by this method from the following ketones, in the yields indicated:

Ketone	*Boiling Point of Aminonitrile* °C	*Yield of Aminonitrile* %
Acetone	49–50/$_{12mm}$	77
Methyl ethyl ketone	....	51–57
Diethyl ketone	70.8–71.7/$_{11mm}$	46
Methyl butyl ketone	86–88/$_{10mm}$	88
Methyl *iso*butyl ketone	77–79/$_{11.5mm}$	63
Pinacoline	....	42
Methyl hexyl ketone	....	55

Jawelow[40] prepared aminonitriles by the same method from the following ketones in the yields indicated:

Ketone	*Yield of Aminonitrile* %
Phenyl methyl ketone	47
p-Tolyl methyl ketone	42
1,2-Xylyl-4-methyl ketone	49
1,3-Xylyl-4-methyl ketone	21
1,4-Xylyl-2-methyl ketone	20
Phenyl ethyl ketone	47
Benzyl acetone	72

Ethyl acetoacetate heated at 70° with an alcoholic solution of ammonium cyanide forms the aminonitrile $CH_3C(CN)(NH_2).CH_2COOC_2H_5$, b.p.$_{10.5}$ = 90–94°, in 54% yield. *Ethyl pyruvate* gives with ammonium cyanide alanine in 32% yield; *ethyl levulinate* forms $CH_3C(CN)(NH_2)CH_2CH_2COOC_2H_5$ in 64% yield. *Ethyl diethylacetylacetate* does not react with ammonium cyanide[97].

Immedörfer[41] prepared, by a similar method, N-methyl-C-diethylglycinonitrile, $CH_3NH.C(C_2H_5)_2CN$, N-methyl-C-methylethylglycinonitrile, $CH_3NH.-C(CH_3)(C_2H_5)CN$, and N-ethyl-C-dimethylglycinonitrile, $C_2H_5NH.C(CH_3)_2.CN$.

Zelinsky and Stadnikoff[42] prepared aminonitriles from a number of ketones by this method and converted these to the corresponding acids. The yield of acids were as follows:

Acid	*Yield* *% of Theory*
Cyclohexylaminoacetic acid, $CH_2.(CH_2)_4CH.CH(NH_2).COOH$	80
1-Methyl-3-aminocyclopentane-3-carboxylic acid, $CH_2CH(CH_3).CH_2.CH_2.C(NH_2).COOH$	59
1-Aminocyclohexane-1-carboxylic acid, $CH_2(CH_2)_4.C(NH_2).COOH$	93
1-Methyl-3-aminocyclohexane-1-carboxylic acid, $CH_2CH(CH_3).(CH_2)_3.C(NH_2).COOH$	52
1-Aminocycloheptane-1-carboxylic acid, $CH_2(CH_2)_5.C(NH_2)COOH$	

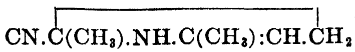
A mixture of hydrocyanic acid and a primary amine H_2NR reacting with the ethyl ester of levulinic acid gives, $CH_3.C(CN)(NHR).CH_2CH_2COOC_2H_5$, or a methylpyrrolidone nitrile[108],

$$CH_3.C(CN).CH_2.CH_2.CO.N.R$$

Acetone reacts with ethylenediamine hydrochloride and potassium cyanide, forming ethylene-bis-α-imino*iso*butyronitrile, $(CH_3)_2C(CN)NHCH_2CH_2NHC(CN)(CH_3)_2$, m.p. 93° (dec.). The nitrile may be hydrolyzed to the corresponding acid[43]. Other aliphatic diamines, $H_2N(CH_2)_nNH_2$, have been condensed to bis-α-iminonitriles with acetone and other ketones and aldehydes[109]. With aniline hydrochloride and potassium cyanide in ligroind, acetone gives α-anilino*iso*butyronitrile[44]; it reacts with hydrazine sulfate and potassium cyanide in concentrated aqueous solution, forming α,α′-hydrazinodi*iso*butyronitrile, $(CH_3)_2C(CN).NH.NH.C(CN)(CH_3)_2$. This compound in cold hydrochloric acid solution is oxidized by bromine water to *i*-azo*iso*butyronitrile, $(CH_3)_2$-$C(CN).N{=}N.C(CN)(CH_3)_2$, which on heating is converted to tetramethylsuccinonitrile[45], $CNC(CH_3)_2C(CH_3)_2CN$. A hydrazino dinitrite has also been prepared from ethyl methyl ketone[106].

Methylallylaminopropionitrile has been prepared from allyl acetone and ammonium cyanide[46].

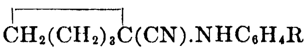
Acetonylacetone reacts in aqueous solution with ammonium chloride and potassium cyanide, forming the compound, $CH_3C(NH_2)(CN).CH_2CH_2COCH_3$, which condenses to[49]



$$CN.C(CH_3).NH.C(CH_3):CH.CH_2$$

Cyclohexanone reacting with potassium cyanide and the hydrochloride of an aromatic amine forms cyclohexanonurylamino cyanide[110].

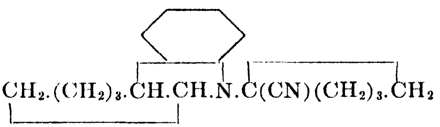
Various substituted 1-anilino-1-cyanocyclopentanes



$$CH_2(CH_2)_3C(CN).NHC_6H_4R$$

have been made by adding an aqueous solution of potassium cyanide to an acetic acid solution of the amine and cyclopentanone[50].

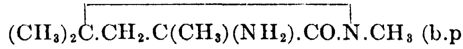
Hexahydrocarbazyl-1-cyanocyclopentane,



$$CH_2.(CH_2)_3.CH.CH.N.C(CN)(CH_2)_3.CH_2$$

prisms melting at 170° forms when an aqueous potassium cyanide solution is added to a solution of hexahydrocarbazol and cyclohexanone in acetic acid. Tetrahydropentindyl-2-cyano-1-cyclopentane, m.p. 51°, forms similarly from cyclopentanone, tetrahydropentindol, and hydrocyanic acid[111].

The aminoketone, $(CH_3)_2C(NHCH_3).CH_2CO.CH_3$, reacting with a mixture of potassium cyanide and ammonium chloride in solution forms the aminonitrile, $(CH_3)_2C(NHCH_3).CH_2.C(NH_2)(CN)CH_3$. On hydrolysis this compound is converted to an aminopyrrolidone,



$$(CH_3)_2C.CH_2.C(CH_3)(NH_2).CO.N.CH_3$$ (b.p. = 140°–143°)

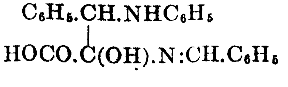
Ammonium chloride may be replaced with methylamine hydrochloride with similar results[112].

Aminonitriles have been prepared from sugars containing a carbonyl group by reaction with a mixture of hydrocyanic acid and the free amine[113].

Aminonitriles from Aromatic Aldehydes and Ketones. Aminophenylacetonitrile forms from benzaldehyde, potassium cyanide and ammonium chloride reacting in ligroin in the presence of a small amount of water[114].

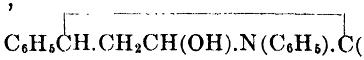
Benzaldehyde reacting in sunlight in the course of seven days with a mixture of ethyl aminoacetate hydrochloride and potassium cyanide forms the compound $C_6H_5CH(CN)NH.CH_2COOC_2H_5.HCl$. The compound $C_6H_5CH(CN)NH.CH(C_6H_5)COOC_2H_5.HCl$ has been prepared similarly from benzaldehyde, ethyl aminophenylacetate hydrochloride and potassium cyanide[115].

Anilinophenylacetonitrile, $C_6H_5CH(CN).NH.C_6H_5$, has been prepared from benzaldehyde, aniline and hydrocyanic acid. With benzaldehyde the compound forms $C_6H_5CH(NH.C_6H_5)CON:CH.C_6H_5$ and[116]



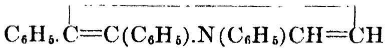
$$\begin{array}{l} C_6H_5.CH.NHC_6H_5 \\ HOCO.C(OH).N:CH.C_6H_5 \end{array}$$

Condensed with cinnamic aldehyde it forms 1,2,3-triphenyl-2-cyano-5-hydroxytetrahydropyrrole[47],



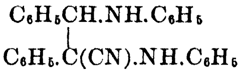
$$C_6H_5CH.CH_2CH(OH).N(C_6H_5).C(CN).C_6H_5$$

In a similar manner, phenyl-*p*-toluidinoacetonitrile may be condensed with cinnamic aldehyde to 1-*p*-tolyl-2,3-diphenyl-5-hydroxydihydropyrrole. These compounds may be converted by refluxing in alcohol and subsequent dehydration to the corresponding pyrrole derivatives. Thus, from triphenylhydroxy tetrahydropyrrole has been obtained 1,2,3-triphenylpyrrole[48],



$$C_6H_5.C{=}C(C_6H_5).N(C_6H_5)CH{=}CH$$

Anilinophenylacetonitrile reacting with benzylidene aniline, $C_6H_5CH{:}N.C_6H_5$, gives μ-cyanohydrobenzoïndianilide[118],



$$\begin{array}{l}C_6H_5CH.NH.C_6H_5\\ C_6H_5.C(CN).NH.C_6H_5\end{array}$$

Benzaldehyde reacting with a mixture of equivalent quantities of hydrazine hydrochloride and potassium cyanide in aqueous solution forms the compound $C_6H_5CH{:}N.NH.CH(CN)C_6H_5$, yellow plates melting at 112°. This reaction does not take place with all aromatic aldehydes.

Salicylaldehyde reacts with ammonium cyanide to form the compound $C_{29}H_{21}N_3O_3$; in alcoholic solution, the compound $C_{22}H_{18}N_2O_4$ forms[63].

p-Methoxyphenylglycinonitrile, $CH_3OC_6H_4CH(NH_2)CN$, m.p. 65°, has been obtained by the action of potassium cyanide and ammonium chloride on anisalidehyde in ethereal solution in the presence of a small amount of water[54].

Surinamin (N-methyltyrosine) has been prepared from *p*-methoxyphenylacetaldehyde by reaction with a solution of methylamine hydrochloride and potassium cyanide and subsequent hydrolysis with hydrochloric acid[53].

$$p\text{-}CH_3OC_6H_4CH_2CHO + CH_3NH_2.HCl + KCN \rightarrow CH_3OC_6H_4.CH_2CH(CN).NH.CH_3 + KCl + H_2O$$

$$CH_3O.C_6H_4.CH_2(CN).NH.CH_3 + 2HCl + 2H_2O \rightarrow HOC_6H_4.CH_2.CH(NHCH_3).COOH + NH_4Cl + CH_3Cl$$

o-Nitrobenzaldehyde does not react with aniline and hydrocyanid acid[56]. The anilidonitrile has been prepared successfully from *o*-nitrobenzaldehyde, potassium cyanide and aniline acetate in glacial acetic acid[57].

The preparation of aminonitriles through the interaction of aldehydes, hydrocyanic acid and three to four fold excess of ammonia is protected by patents[122].

Acetophenone reacts at 80° with ammonium cyanide to form *aminophenylpropionitrile* in 47% yield. The product is unstable and difficult to isolate in a pure form. Aminonitriles have also been prepared by the interaction of ammonium cyanide and *p*-methylacetophenone, 3,4-, 2,4- and 2,6-dimethylacetophenone, methyl ethyl ketone and 2-phenylethyl methyl ketone. On attempted reduction with sodium and alcohol, the CN group is eliminated from these aminonitriles as sodium cyanide[98]. *Benzophenone* and *p-tolyl phenyl ketone* do not react with ammonium cyanide[99].

Ammonium cyanide reacts with *benzil* to form benzamide and benzaldehyde cyanohydrin:

$$C_6H_5CO.COC_6H_5 + NH_5CN \rightarrow G_6H_5CONH_2 + C_6H_5CH(OH)CN$$

Anisil, *piperil*, *m-dinitrobenzil*, and *furil* react in a similar manner. *Benzoïn* and *benzoyl acetone* do not react with ammonium cyanide[100].

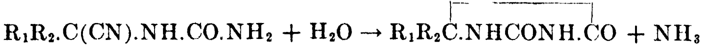
Herbst and Johnson[58] have prepared the following aminonitrile hydrochlorides from the corresponding ketones and ammonium cyanide in the yields indicated:

	M.P. °*C*	*Yield,* %
$C_6H_5CH_2\overset{CH_3}{\dot{C}}.(CN).NH_2.HCl$	148–150	86.5
$C_6H_5CH_2.\overset{C_2H_5}{\dot{C}}.(CN).NH_2.HCl$	135–140	81
$C_6H_5CH_2.CH_2\overset{CH_3}{\dot{C}}(CN).NH_2.HCl$	140–141	88
$C_6H_5CH_2CH_2\overset{C_2H_5}{\dot{C}}.(CN).NH_2.HCl$	84	85
$\overline{CH_2CH_2CH_2CH_2CH_2CH}.(CN)NH_2.HCl$	202–204	77

The nitriles were converted to the corresponding ureids by reaction with potassium cyanate in 50% acetic acid solution:

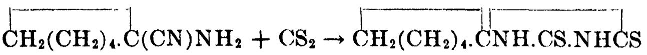
$$R_1R_2C(CN).NH_2 + KCNO + HOCOCH_3 \rightarrow R_1R_2C(CN).NH.CO.NH_2 + KOCOCH_3$$

The ureids were finally converted to hydantoins:



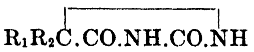
$$R_1R_2.C(CN).NH.CO.NH_2 + H_2O \rightarrow \overline{R_1R_2C.NHCONH.CO} + NH_3$$

Aminonitriles have been prepared from *cyclopentanone*, *cyclohexanone*, *p-methylcyclohexanone*, *3-methylcyclopentanone* and *l-menthone*. From these nitriles, methylene-spiro-2,4-dithiohydantoins have been obtained by reaction with carbon disulfide[59]:



$$\overline{CH_2(CH_2)_4.C}(CN)NH_2 + CS_2 \rightarrow \overline{CH_2(CH_2)_4.C}\overline{NH.CS.NHCS}$$

Bucherer and associates[123] demonstrated that α-amononitriles, $R_1R_2C(NH_2)$-CN, reacting with carbon dioxide give hydantoins of the type



$$R_1R_2\overline{C.CO.NH.CO.NH}$$

It was demonstrated that hydantoins may be obtained directly from cyanohydrins and ammonium carbonate, or from the carbonyl compound, potassium cyanide and ammonium carbonate. An aminonitrile seems to be the intermediate product in the last two cases.

The reaction of the carbonyl compound with potassium cyanide and ammonium carbonate proceeds best in 50% aqueous alcohol and at 50° to 60°. It is necessary in many cases to heat the reaction mixture for eight hours or more. An improvement in yield may be brought about in some instances by the use of the bisulfite compound of the ketone or aldehyde, and occasionally merely by the addition of some sodium bisulfite to the reaction mixture.

Ketones generally give good yields of the hydantoin, but aldehydes tend to react in another direction. The yield of hydantoin from various carbonyl compounds is given in the following table:

Carbonyl Compound	*Yield of Hydantoin, %*	*Carbonyl Compound*	*Yield of Hydantoin, %*
Acetone	80	Phenylacetone	80
Cyclohexanone	95	Diphenylacetone	?
Methyl ethyl ketone	90	Benzaldehyde	20
Acetophenone	90	Phenylacetaldehyde	15
Phenyl ethyl ketone	80-85	Acetoacetic ester	0

High yields of hydantoins were obtained when the bisulfite compounds of benzaldehyde, phenylacetaldehyde and acetoacetic ester were substituted for the free aldehydes. Benzil, $C_6H_5COCOC_6H_5$, and phenylmethyl-1,2-diketone reacted as though they were first split to benzaldehyde, and yielded 5-phenylhydantoin. Acetaldehyde and formaldehyde react in another direction and do not form hydantoins. Acetylacetone, benzoïn, benzophenone and camphor do not react.

Attempts to prepare N-substituted hydantoins by use of amines and carbon dioxide, and by other modifications of the reaction failed. Efforts to prepare thiohydantoins by substituting CS_2 for CO_2 were equally unsuccessful. The reaction in this instance led to the formation of tetrahydrothiazolonimine derivatives,

$$R_1R_2C.C(:NH).S.C(R_1)(R_2)NH$$

Henze and co-workers[124] prepare a large number of 5,5-substituted hydantoins of various types by use of Bucherer's reaction, *i.e.* through the interaction of various ketones with potassium cyanide and ammonium carbonate in 50% aqueous alcohol. With few exceptions the yield of hydantoin was quite good, often in excess of 70% of theory.

Aminonitriles from Amino Compounds of Aldehydes and Ketones

Formaldehyde reacts with *anthranilic acid* to form a monomethylol derivative which reacts with potassium cyanide giving *anthraniloacetonitrile* in theoretical yield:

$$C_6H_5(COOH).NH_2 + H_2CO \rightarrow C_6H_5.(COOH).NH.CH_2OH$$
$$C_6H_5(COOH).NH.CH_2OH + KCN \rightarrow C_6H_5(COOK).NH.CH_2CN + H_2O$$

This compound may be converted in steps to phenylglycine-*o*-carboxylic acid, indoxylic acid, indoxyl and finally *indigo.* These reactions form the basis of a commercial method of preparation of indigo.

Methylenemethylimine reacts with hydrocyanic acid to form *N-methylglycinonitrile:*

$$CH_2:N.CH_3 + HCN \rightarrow CN.CH_2.NH.CH_3$$

Hydrocyanic acid reacts with *methyleneiminoacetonitrile* in the presence of hydrochloric acid to form *iminodiacetonitrile,* $HN(CH_2CN)_2$, m.p. 75°[101]. This compound condenses with cyanic acid forming hydantoinacetic acid,

$$CO.NHCO.CH_2.N.CH_2.COOH$$

Condensation with *iso*thiocyanates leads to the formation of thio-2-hydantoin-acetic acid[102].

Delépine[60] considered that the reaction between *aldehyde ammonia* (or ethylidineimine, $CH_3CH{:}NH$) and hydrocyanic acid proceeded as follows:

$$4(CH_3CH{:}NH.H_2O) + 3HCN \rightarrow 2CH_3.CH(NH_2).CN + NH_4CN + [CH_3.CH.(CN)]_2NH + 4H_2O$$

Passavant[61] believed that α-aminopropionitrile is the first product of the reaction, and that the secondary and tertiary compounds, $CH_3CH(CN).NH.CH(CN)CH_3$ and $N[CH(CH_3).CN]_3$, are formed from this by loss of ammonia.

Hydrocyanic acid reacts with *ethyleneimine* giving *α-aminopropionitrile* and *di-α-cyanethylamine*[62]:

$$4CH_3.CH{:}NH + 5HCN \rightarrow 2NH_2\,CH(CN).CH_3 + NH[CH(CN)CH_3]_2 + NH_4CN$$

Hydrocyanic acid reacts with *Schiff bases*, $R_1N{:}CH.R_2$, forming compounds of the type $R_1NH.CH(CN).R_2$. With most Schiff bases, the reaction takes place with ease, but some react with difficulty. Pyrotartaric acid anilide forms an exception, failing to react with hydrocyanic acid, while the anilide of benzoin adds hydrocyanic acid with difficulty[63].

Hydrazones and *oximes* of *aliphatic aldehydes* or *ketones* react with hydrocyanic acid in a similar manner, but those of the aromatic series do not. Thus, *acetaldoxime* forms α-hydroxylaminopropionitrile, $CH_3CH(CN).NHOH$, and *acetoxime* forms α-hydroxylamino*iso*butyronitrile[64], $(CH_3)_2.C(NHOH).CN$. *Acetaldehyde phenylhydrazone* reacts with hydrocyanic acid, forming α-phenylhydrazino-propionitrile[64]:

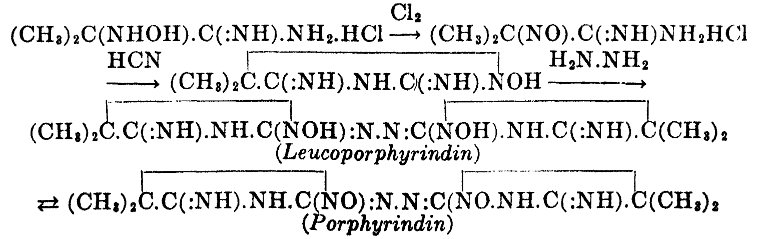
$$CH_3C{:}N\,NHC_6H_5 + HCN \rightarrow CH_3CH(CN).NH.NHC_6H_5$$

Chloralacetamide reacts with hydrocyanic acid, forming *chloral cyanohydrin*[34].

α-Hydroxylaminoisobutyronitrile (m.p. 100°) has been prepared from *acetoxime*, potassium acid phosphate and sodium cyanide in aqueous solution[65]:

$$(CH_3)_2C{:}NOH + HCN \rightarrow (CH_3)_2C(CN).NHOH$$

From this compound, porphyrindin has been prepared by the following steps[66]:



$$(CH_3)_2C(CN).NHOH \xrightarrow{C_2H_5OH\,+\,HCl} (CH_3)_2C(NHOH).C({:}NH).OC_2H_5.HCl \xrightarrow{NH_3}$$

$$(CH_3)_2C(NHOH).C({:}NH).NH_2.HCl \xrightarrow{Cl_2} (CH_3)_2C(NO).C({:}NH)NH_2HCl$$

$$\xrightarrow{HCN} (CH_3)_2C.C({:}NH).NH.C({:}NH).NOH \xrightarrow{H_2N.NH_2}$$

$$(CH_3)_2C.C({:}NH).NH.C(NOH){:}N.N{:}C(NOH).NH.C({:}NH).C(CH_3)_2$$

(*Leucoporphyrindin*)

$$\rightleftarrows (CH_3)_2C.C({:}NH).NH.C(NO){:}N.N{:}C(NO.NH.C({:}NH).C(CH_3)_2$$

(*Porphyrindin*)

α-Hydroxylamino*iso*butyronitrile is oxidized by chlorine to α-nitroso*iso*butyronitrile, $(CH_3)_2C(NO).CN$, m.p. about 53°, an unstable compound, insoluble in water and difficulty soluble in alcohol. It is converted quantitatively to the corresponding amide (m.p. 158°) by the action of concentrated hydrochloric acid at 0°[67].

The imino ethyl ether related to hydroxylamino *iso*butyronitrile, $(CH_3)_2$-$C(NHOH).C(:NH)OC_2H_5$, and the corresponding amidine hydrochloride, $(CH_3)_2$-$C(NHOH).C(:NH)NH_2.HCl$, have been prepared from *α-hydroxylaminoisobutyronitrile*, and these compounds have been converted to the corresponding nitroso compound by the action of chlorine[67].

Methyl ethyl ketoxime reacts with hydrocyanic acid to form α-hydroxylamino-α-methylbutyronitrile[68]:

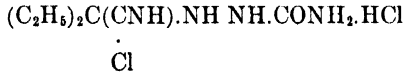
$$CH_3C(:NOH).C_2H_5 + HCN \rightarrow CH_3C(CN)(NHOH).C_2H_5$$

Hydrocyanic acid, reacting with *aldehyde semicarbazone*, forms hydrazopropionic nitrile[103], $CH_3CH(CN).NH.NH.CONH_2$; hydrazo*iso*butyronitrile is similarly obtained from *acetone semicarbazone* and hydrocyanic acid. Concentrated hydrochloric acid converts hydrazo*iso*butyronitrile to the corresponding amide and the diamide; complete hydrolysis gives α-hydrazino*iso*butyric acid[104].

Diethyl ketone semicarbazone reacts with hydrocyanic acid to form α-ethyl-α-semicarbazidobutyronitrile:

$$(C_2H_5)_2C:N.NH.CONH_2 + HCN \rightarrow (C_2H_5)_2.C(CN).NH.NHCO.NH_2$$

This compound is decomposed by acids and alkalies and, therefore, cannot be hydrolyzed to the corresponding acid. The imidochloride,



$$\underset{\displaystyle Cl}{(C_2H_5)_2C(CNH).NH\,NH.CONH_2.HCl}$$

has been obtained as a crystalline, white powder[69].

Triisobutylidinediamine, $C_4H_8:N.C_4H_8N:C_4H_8$, reacts with hydrocyanic acid to form the dinitrile,[70] $CNC_4H_8.NH.C_4H_8NH.C_4H_8CN$.

Hexamethylenetetramine reacts with hydrocyanic acid in the presence of hydrochloric acid to form tri-(cyanomethyl)-amine-(nitriloacetonitrile) hydrochloride:

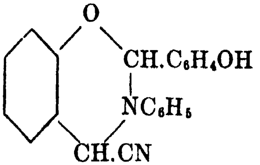
$$C_6H_{12}N_4 + 6HCN + 4HCl \rightarrow 2(CNCH_2)_3N.HCl + 2NH_4Cl$$

In the absence of hydrogen chloride, dicyanomethylamine forms[71]:

$$C_6H_{12}N_4 + 6HCN \rightarrow 3(CNCH_2)_2.NH + NH_3$$

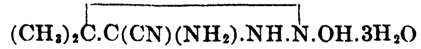
Auramine $((CH_3)_2NC_6H_4)_2C{=}NH.HCl$, reacting with potassium cyanide is converted to hydrocyanoauramine[119], $[(CG_3)_2NC_6H_4]_2C(CN).NH_2$.

Slicylideneaniline reacts with potassium cyanide in absolute alcoholic solution to form the compound



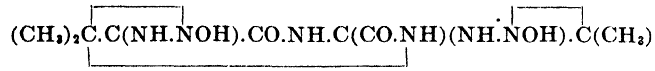
melting at 155°[120].

Nitrosoisobutyramidine reacts with potassium cyanide in aqueous solution at 50° to form a cyano derivative of the probable structure



$$(CH_3)_2C.C(CN)(NH_2).NH.N.OH.3H_2O$$

in 80% yield, melting with decomposition at 248–250° and giving, on hydrolysis with concentrated hydrochloric acid at 100°, an inner amido anhydride[72]:



$$(CH_3)_2C.C(NH.NOH).CO.NH.C(CO.NH)(NH.NOH).C(CH_3)_2$$

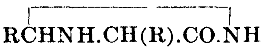
Benzylideneaniline reacts with hydrocyanic acid to form α-anilino-α-phenylacetonitrile,

$$C_6H_5CH{:}NC_6H_5 + HCN \rightarrow C_6H_5CH(CN).NH.C_6H_5$$

Dibenzylidenephenylmethylenediamine, $C_6H_5CH.(N{:}CHC_6H_5)_2$, reacts with hydrocyanic acid to form the compound[73] $C_6H_5CH.[NH.CH(CN).C_6H_5]_2$. The reaction is general for aromatic compounds of this type:

$$RCH.(N{:}CHR)_2 + 2HCN \rightarrow RCH[NH.CH(CN)R]_2$$

The monocyano compound, $RCH(CN).NH.CH(R).N{:}CHR$, is also formed. The latter is hydrolyzed by aqueous hydrochloric acid to:



$$RCHNH.CH(R).CO.NH$$

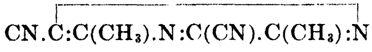
the dicyano compound being hydrolyzed to[74]: $RCH(CN).NH_2$ and $R.CHO$. The compounds, $RCH.(N{:}CHR)_2$, are prepared by the condensation of aromatic aldehydes, $RCHO$, with ammonia.

Benzalazine reacts with hydrogen cyanide in glacial acetic acid to form phenylbenzalhydrazoneacetonitrile[75]:

$$C_6H_5CH{:}N.N{:}CHC_6H_5 + HCN \rightarrow C_6H_5CH{:}N.NH.CH(CN).C_6H_5$$

Miller and Plöchl[76] observed that compounds of the type, $RCH{:}N.R$, are capable of adding hydrocyanic acid if they are symmetrical with regard to nitrogen, *i.e.*, when the valencies of nitrogen are in the same plane.

2,5-Dimethyl-3,6-dicyanopyrazine,



$$CN.C{:}C(CH_3).N{:}C(CN).C(CH_3){:}N$$ (m.p. 207°)

has been obtained through the interaction of potassium cyanide and the bisulfite compound of *isonitrosoacetone*, $CH_3.CO.CH{:}NOH$. The phenyl analog of this compound has also been prepared from the bisulfite compound of *isonitrosoacetophenone* and potassium cyanide[105].

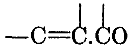
Aminonitriles from Bisulfite Compounds of Aldehydes and Ketones

Aminonitriles may be prepared from the bisulfite compounds of aldehydes by adding the amine in slight excess to the aqueous solution of the bisulfite compound, then adding a concentrated aqueous solution of potassium cyanide[77].

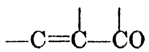
In preparing phenylaminoacetonitrile, Knoevenagel proceeded as follows:

> A mixture of 15 parts of 40% formaldehyde solution and 55 parts of 38% aqueous solution of sodium bisulfite was heated on a water bath, and 18.5 parts of aniline were added under agitation. Stirring was continued for a few minutes, then a solution of 13 parts of potassium cyanide in water was added. On gentle warming, phenylaminoacetonitrile separated out as an oil in an almost quantitative yield.

Knoevenagel showed that the groups

$=C=O$, 
$-C{=}\overset{|}{C}.\overset{|}{C}O$ and $RC{=}NR'$

react with sodium bisulfite, addition taking place in the case of compounds containing the


$-C{=}\overset{|}{C}{-}\overset{|}{C}O$

group at the C,C double bond. The group, $RC{=}NR'$, is converted by treatment with sodium bisulfite to: $RC(SO_3Na).NHR$. Amides of sulfonic acids, RSO_2NH_2, react with the bisulfide compound of formaldehyde giving the compounds $RCONHCH_2SO_3Na$ and $RSO_2NHCH_2SO_3Na$; these, reacting with potassium cyanide, form the sulfonamido nitriles[79] $RSO_2NH.CH_2.CN$.

Knoevenagel and Mercklin[77] prepared the following aminonitriles in the yields indicated:

	Boiling Point, °C	*Yield, %*
Diethylaminoacetonitrile	$62.5^\circ/_{14\text{ mm}}$	almost quantitative
α-Diethylaminopropionitrile	$68/_{17\text{ mm}}$	80
α-Diethylamino-α-*iso*butylacetonitrile	$88.5\text{–}89/_{11\text{ mm}}$	92
α-Diethylamino-*n*-capronitrile	$125\text{–}126/_{11\text{ mm}}$	86
α-Diethylaminobenzyl cyanide	$130\text{–}131/_{11\text{ mm}}$	76
α-Diethylamino-*p*-methoxybenzyl cyanide	$166/_{11\text{ mm}}$ m.p. 44°	75
Methylene ether of 3,4-dihydroxyphenyl diethylaminoacetonitrile, $CH_2O_2C_6H_3\text{-}CH[N(C_2H_5)_2].CN$	$179.5/_{12\cdot5\text{ mm}}$	81
Ethylaminoacetonitrile	$81\text{–}83/_{29\text{ mm}}$	70
Ethylimino-bis-acetonitrile, $CN.CH_2N\text{-}(C_2H_5)CH_2CN$	$141/_{13\text{ mm}}$	73
α-Ethylamino*iso*butylacetonitrile	$83.5\text{–}84/_{12\text{ mm}}$	84
Ethylamino-*n*-caprylonitrile	$122/_{12\text{ mm}}$	94

Knoevenagel[78] prepared, in addition, the following by the same method:

	Melting Point °*C*	*Yield*, %
p-Tolylaminoacetonitrile	57	
m-Xylylaminoacetonitrile	50–52	
α-Naphthylaminoacetonitrile	44–45	
β-Naphthylaminoacetonitrile	82–85	
o-Carboxyphenylaminoacetonitrile	182–184(dec.)	
o-Chlorophenylaminoacetonitrile	b.p.$_{14}$ 174–175°	
Piperidinoacetonitrile	18–19	80
α-Piperidinopropionitrile	b.p.$_{12.5}$ 93–94°	76
Anilinophenylacetonitrile	85	85
Anilino-*o*-hydroxyphenylacetonitrile	113–114	65
Anilino-*p*-*iso*propylacetonitrile	86	84
Anilino-*p*-methoxyphenylacetonitrile	104–105	
Methoxyphenylaminophenylacetonitrile	63–64	
α-Piperidinophenylacetonitrile	62–63	nearly quantitative
α-Piperidino-*o*-hydroxyphenylacetonitrile	89–90	70
α-Piperidino-*p*-methoxyphenylacetonitrile	75–76	80
α-Piperidinostyrylacetonitrile	98–99	75

By the same method have also been prepared methylphenylaminoacetonitrile, m.p. 13° b.p.$_{13}$ 148–149°, ethylphenylaminoacetonitrile, m.p. 21°, b.p.$_{13}$ 150–151°, phenylbenzylaminoacetonitrile. Bucherer and Grolée[16] prepared phenylhydrazido*iso*butyronitrile, m.p. 70°, α-and-β-naphthylamino*iso*butyronitriles, m.p. 106–107° and 119°, also $C_6H_5NH.NHC(CN)(CH_3).CH_2COOH$, m.p. 63–64°.

Bucherer and Schwalbe[80] prepared the following compounds by the bisulfite method:

	Melting Point °*C*	*Yield*, %
ω-Cyanomethylaniline, $C_6H_5NH.CH_2CN$	....	95.4–98
ω-Cyanomethyl-*o*-toluidine		
ω-Cyanomethyl-*o*-anisidine	68	
Di-ω-cyanodimethyl-*m*-toluylenediamine	207	81
ω-Cyanomonomethyl-*p*-phenylenediamine	168	
Di-ω-cyanodimethylbenzidine	241–242	85
ω-Cyanomonomethylbenzidine	142–144	
ω-Cyanomethylanthranilic acid	184	99.8
ω-Cyanomethylnaphthionic acid salt of sodium	258 (turn brown)	63
ω-Cyano-methyl α-naphthylamine	92	75
ω-Cyanomethyl-β-naphthylamine	102–104	85
ω-Cyanobenzylaniline	....	89
ω-Cyanobenzyl-*o*-toluidine	71	60
ω-Cyanobenzyl-*o*-anisidine	73	84
ω-Cyanobenzylanthranilic acid	166	91
ω-Cyanobenzyl-β-naphthylamine	119	89
Di-ω-cyanobenzyl-*p*-phenylenediamine	162	88

Luten[81] prepared the following aminonitriles also from bisulfite compounds of the corresponding aldehydes or ketones in the yields indicated:

	B.P. °C	*Under* mm	*Yield,* %
$(CH_3)_2N.CH_2.CN$	137		45–79
$(C_2H_5)_2N.CH_2.CN$	70	23	70–75
$(n\text{-}C_3H_7)_2N.CH_2.CN$	96	23	72
$(i\text{-}C_3H_7)_2N.CH_2.CN$	78	14	52–65
$(n\text{-}C_4H_9)_2N.CH_2CN$	85	4	75
$(i\text{-}C_4H_9)_2N.CH_2.CN$	87	9	75
$(n\text{-}C_5H_{11})N.CH_2.CN$	102–104	4	84
$(i\text{-}C_5H_{11})N.CH_2.CN$	93–94	4	79
$(n\text{-}C_8H_{17})N.CH_2.CN$	145–150	3	31
$(CH_3)_2N.CH(CH_3).CN$	59–61	40	28
$(C_2H_5)_2N.CH(CH_3).CN$	51	11	68
$(CH_3)_2N.CH(C_2H_5).CN$	67–68	23	78
$(C_2H_5)_2N.CH.(C_2H_5).CN$	75.5	16	25
$(CH_3)_2N.C(CH_3)_2CN$	57	25	52–69
$(CH_3)(C_2H_5)N.C(CH_3)_2.CN$	58	14	53
$(C_2H_5)_2N.C(CH_3)_2.CN$	72–74	14	30–39
$(CH_3)_2N.CH(n\text{-}C_3H_7).CN$	70	14	
$(C_2H_5)_2N.CH.(n\text{-}C_3H_7).CN$	95	15	44
$(CH_3)_2N.(CH(i\text{-}C_3H_7).CN$	61	14	
$(C_2H_5)_2N.CH(i\text{-}C_3H_7).CN$	69	4	39
$(CH_3)_2N.C(CH_3)(C_2H_5).CN$	63	12	70
$(C_2H_5)_2.N(CH_3)(C_2H_5).CN$	78	16	18
$(C_2H_5)_2N\ CH(n\text{-}C_4H_9).CN$	91	9	64
$(CH_3)_2N.C(CH_3)(n\text{-}C_3H_7).CN$	75	10	49
$(C_2H_5)_2N.C(CH_3)(n\text{-}C_3H_7).CN$	103	21	11.3
$(CH_3)_2N.C(CH_3)(i\text{-}C_3H_7).CN$	63	7	42
$(CH_3)_2N.C(C_2H_5)_2.CN$	69–73	10	40
$(C_2H_5)_2N.CH(n\text{-}C_6H_{13}).CN$	113–115	13	73
$(CH_3)_2N.C(CH_3)(n\text{-}C_5H_{11}).CN$	104–105	10	63
$(CH_3)(C_6H_5)N.CH_2CN$	138–141	9	70–76
$(CH_3)_2N.CH.(C_6H_5).CN$	90	6	29
$(C_2H_5)_2N.CH(C_6H_5).CN$	122–124	9	56
$\overline{CH_2CH_2CH_2CH_2CH_2N}.CH_2.CN$	83	9	94

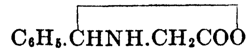
Luten prepared quaternary ammonium compounds from these aminonitriles.

Zelinsky and Dengin[82] prepared the following aminonitriles: α-amino-α-methyl-β-hydroxypropionitrile, $HOCH_2.C(CH_3)(NH_2).CN$; α-amino-α-methyl-γ-hydroxy-*n*-valeric nitrile, $CH_3.CH(OH).CH_2C(CH_3).NH_2.CN$, α-amino-α-methyl-δ-hydroxy-*n*-valeronitrile, $HO.CH_2.CH_2.CH_2.C(CH_3)(NH_2).CN$, α-amino-α-methyl-ε-hydroxy-*n*-capronitrile, $HO.CH_2.CH_2.CH_2.CH_2.C(CH_3)(NH_2).CN$

Aminonitriles have also been prepared from the bisulfite compound of ***benzaldehyde*** and ***glycine ethyl ester***,

$$C_6H_5.CH(OH).SO_3K + H_2NCH_2.COOC_2H_5 + KCN \rightarrow C_6H_5.CH(CN).NH.CH_2.COOC_2H_5 + K_2SO_3 + H_2O$$

Under the action of alcoholic caustic, these compounds form benzylidene glycine[83],

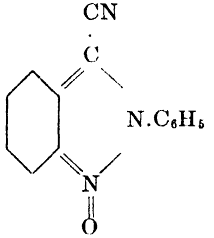


$$C_6H_5.CHNH.CH_2COO$$

o-Nitrophenylanilidoacetonitrile, (m.p. 140°) has been prepared from the bisulfite compound of *o-nitrobenzylideneaniline:*

$$(o)NO_2.C_6H_4.CH(:N.C_6H_5)HSO_3Na + NaCN \rightarrow NO_2C_6H_4.CH(CN).NH.C_6H_5 + Na_2SO_3$$

When heated with aqueous solutions of mineral acids, the compound undergoes decomposition; when it is heated with normal sodium carbonate solution, it is converted to 2-phenyl-3-cyanoindazole-N¹ oxide[84],



The amino group in α-aminonitriles may be replaced by an anilido group or other primary aromatic amino-residue by heating a mixture of the nitrile and the aromatic amine in aqueous or alcoholic solution[85],

$$R_1R_2C(CN).NH_2 + H_2NC_6H_5 \rightarrow R_1R_2C(CN).NH.C_6H_5 + NH_3$$

Anilido acetonitrile results from the reaction of monochloracetonitrile and aniline[86].

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Chapter 11

Reaction of Unsaturated Compounds with Hydrocyanic Acid and Alkali Cyanides

Reaction with Hydrocyanic Acid

Hydrocyanic acid and alkali cyanides do not readily react, in general, with unsaturated hydrocarbons. Low yields of nitriles have been obtained through the interaction of hydrocyanic acid with olefins under 1000 pounds of pressure and in the temperature range of 200–400°, in the presence of metallic catalysts such as cobalt or copper[1]. Reaction between *acetylene* and gaseous hydrocyanic acid takes place only at 400–500° in the presence of active carbon impregnated with barium cyanide as a catalyst, and a low yield of vinyl cyanide results[2]. Meyer and Tanzen obtained pyridine in poor yield by heating a mixture of acetylene, hydrocyanic acid and hydrogen at 800–950° in an iron tube. By substituting illuminating gas for acetylene, they obtained a mixture of homologs of pyridine.

Hydrocyanic acid reacts with *unsym*-diphenylethylene in the presence of aluminum chloride forming α,α-diphenylpropionitrile[3]:

$$(C_6H_5)_2C{:}CH_2 + HCN \rightarrow (C_6H_5)_2.C(CN).CH_3$$

Simultaneously a considerable proportion of 1,1,3,3-tetraphenylcyclobutane is formed.

Acetylene reacts at moderate temperature with hydrocyanic acid in the presence of a solution of cuprous chloride and ammonium chloride, forming vinyl cyanide in excellent yield[4]. Substituted acetylenes react similarly[4].

The presence of negative groups in an unsaturated compound may affect the reactivity of the multiple bonds to the point of rendering them capable of reaction with hydrocyanic acid. Thus, hydrocyanic acid generated through the interaction of potassium cyanide and acetic acid, reacts with *ω-benzalacetophenone* in alcoholic solution to form α-phenyl-β-benzoylpropionitrile[5]:

$$C_6H_5.CH{:}CH.CO.C_6H_5 + HCN \rightarrow C_6H_5CH(CN).CH_2.CO.C_6H_5$$

Similarly, *ω-nitrostyrene*, $C_6H_5CH{:}CH.NO_2$, and *nitrocamphene* add one molecule of hydrocyanic acid[6]. *Benzylidenebenzyl cyanide* reacts in presence of potassium cyanide similarly to form diphenylsuccinonitrile[7]:

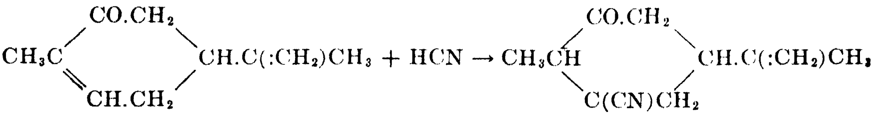
$$C_6H_5CH{:}C(CN)C_6H_5 + HCN \rightarrow C_6H_5CH(CN)CH(CN).C_6H_5$$

α-Phenyl-*para*- and α-phenyl-*o*-nitrocinnamonitriles do not fix hydrocyanic acid; the corresponding *α-meta* compound fixes one molecule of hydrocyanic acid forming the dinitrile.[22]

The reaction of hydrocyanic acid with *α-cyanoacrylates* is exceedingly slow; it is accelerated by cyanide ions in proportion to the concentration of these ions[8].

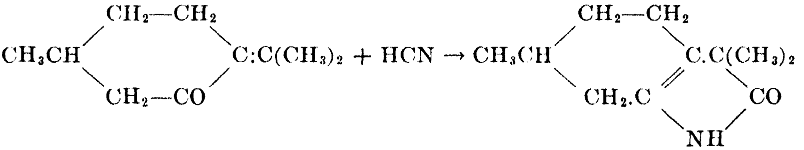
Lapworth[9] prepared a cyanocyanohydrin, $C_{11}H_{18}ON_2$, by the action of hydrocyanic acid on phorone in alcoholic solution in the presence of KCN at 100°

Carvone reacts with hydrocyanic acid forming cyanohydrocarvone:

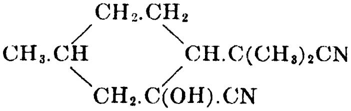


The same compound is also obtained by the action of aqueous potassium cyanide on carvone. Hydrocyanic acid reacts with *cyanohydrocarvone* in the presence of a trace of potassium cyanide to form cyanohydrocarvone cyanohydrin[10].

Pulegone reacts with hydrocyanic acid forming a cyclic amide as follows:



Addition of a second molecule of hydrocyanic acid leads to the formation of the compound[11]:



Hydrocyanic acid adds at the double bond of *isocrotonic acid* to form β-cyanobutyric acid:

$$CH_3CH{:}CH.COOH + HCN \rightarrow CH_3CH(CN).CH_2.COOH$$

The reaction is catalyzed by primary or secondary bases[12]. *Benzalmalonic acid esters* react in a similar manner[13]:

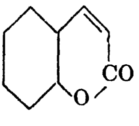
$$C_6H_5CH{:}C(COOC_2H_5)_2 + HCN \rightarrow C_6H_5CH(CN)CH(COOC_2H_5)_2$$

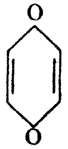
Methyl cinnamylidenemaleate, $C_6H_5CH{:}CH.CH{:}C(COOCH_3)_2$, adds hydrocyanic acid in stages first forming $C_6H_5CH(CN).CH_2CH{:}C(COOCH_3)_2$, then finally[14] $C_6H_5CH(CN)CH_2CH(CN).CH(COOCH_3)_2$.

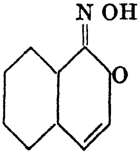
Dihydroresorcinol reacting with nascent hydrocyanic acid at 0° gives 1,3-dihydroxyhexahydro*iso*phthalonitrile[42].

Hydrocyanic acid adds similarly to the ethylenic bond in the following compounds[15,16,17,18,19]:

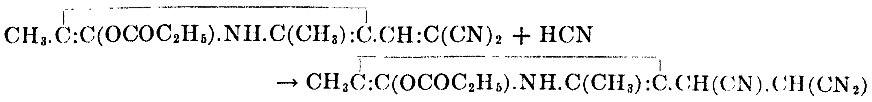
R.CH:CHCN, RC:C(R).CN,







Hydrocyanic acid adds to 2,4-dimethyl-5-carbethoxy-3-ω-dicyanovinylpyrrole to form a tricyano compound:



$$CH_3.\overset{|}{C}:C(OCOC_2H_5).NH.C(CH_3):\overset{|}{C}.CH:C(CN)_2 + HCN \rightarrow CH_3\overset{|}{C}:C(OCOC_2H_5).NH.C(CH_3):\overset{|}{C}.CH(CN).CH(CN_2)$$

The compound is of acidic character. Alcoholic hydrochloric acid hydrolyzes only one of the CN-groups to a carboxyl group[20].

Hydrocyanic acid adds at the double bond of the condensation product of malononitrile and aldehydes:

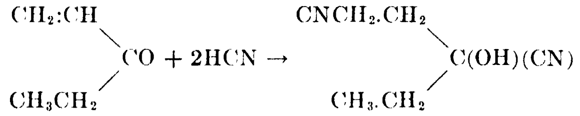
$$RCH:C(CN)_2 + HCN \rightarrow RCH(CN).CH(CN)_2$$

The resulting compounds yield on hydrolysis substituted succinic acids, RCH-(COOH).CH.COOH. Similar addition compounds may be obtained from the condensation product of sodium cyanoacetate and benzaldehyde, or substituted benzaldehydes[21]; also from the condensation product of *p*-methoxybenzaldehyde with benzyl cyanide[22] and aldehydes with acetoacetic esters[23].

Hydrocyanic acid reacts with *mesityl oxide* to form cyano*iso*butyl methyl ketone cyanohydrin[24]:

$$(CH_3)_2C:CH.COCH_3 + 2HCN \rightarrow (CH_3)_2C(CN).CH_2C(OH)(CN)CH_3$$

It reacts with *vinyl acetate* forming cyanoethyl acetate, $CH_3.COOCH(CN).CH_3$. *Vinyl ethyl ketone* gives cyanoethyl ethyl ketone cyanohydrin[25]:

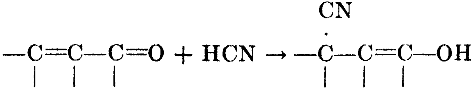


Interaction of one molecule of hydrocyanic acid with one of *vinyl methyl ketone* leads to the formation of levulinonitrile[26]:

$$CH_3CO.CH:CH_2 + HCN \rightarrow CH_3CO.CH_2.CH_2CN$$

The reaction is best carried out at 10 to 40°.

Unsaturated carbonyl compounds, in which the unsaturated bond is in the 2,3 position with respect to the carbonyl group react with hydrocyanic acid to form 3-cyano substituted enelic compounds:



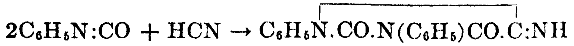
$$-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=O + HCN \rightarrow -\underset{|}{\overset{CN}{C}}-\underset{|}{C}=\underset{|}{C}-OH$$

Propiolic acid esters react with hydrocyanic acid forming β-cyanoacrylic esters[27].

Phenyl isocyanate, reacting with hydrocyanic acid in the presence of a trace of alkali in an inert solvent and under cooling, forms cyanoformanilide[28]:

$$C_6H_5N:CO + HCN \rightarrow C_6H_5NH.CO.CN$$

The reaction proceeds otherwise if carried out in the absence of a diluent and without cooling; in that case 1,3-diphenylparabanic acid-4-imide forms:



$$\mathrm{2C_6H_5N{:}CO + HCN \rightarrow \overbrace{C_6H_5N.CO.N(C_6H_5)CO.C}{:}NH}$$

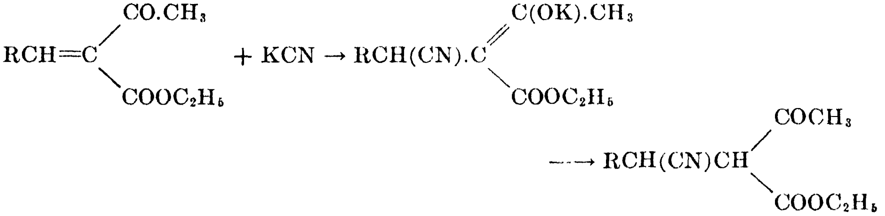
Carbodianyl, reacting with hydrocyanic acid, forms cyanoformic acid diphenylamidine:

$$\mathrm{C_6H_5N{:}C{:}NC_6H_5 + HCN \rightarrow C_6H_5NHC(CN){:}NC_6H_5}$$

Reaction with Alkali Cyanides

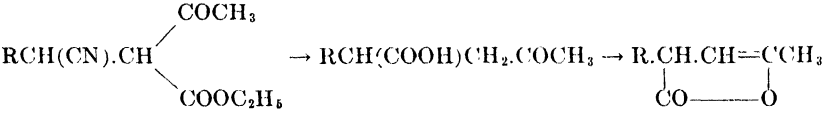
The reaction of aqueous potassium cyanide with *allyl iodide* has been mentioned previously. The entrance of the CN-group at the β-position in the molecule may be considered to follow the hydrolysis of potassium cyanide to KOH and HCN, the latter then adding at the unsaturated linkage.

In aqueous alcoholic solution potassium cyanide reacts with *ethyl ethylidene-* and *butylideneacetoacetates* to form saturated nitriles, the reaction presumably proceeding by the following steps:



$$\mathrm{RCH{=}C\begin{array}{l}\diagup CO.CH_3\\ \diagdown COOC_2H_5\end{array} + KCN \rightarrow RCH(CN).C\begin{array}{l}/\!\!/ C(OK).CH_3\\ \diagdown COOC_2H_5\end{array} \longrightarrow RCH(CN)CH\begin{array}{l}\diagup COCH_3\\ \diagdown COOC_2H_5\end{array}}$$

These nitriles may be simultaneously hydrolyzed and decarboxylated by refluxing with hydrochloric acid[30]:



$$\mathrm{RCH(CN).CH\begin{array}{l}\diagup COCH_3\\ \diagdown COOC_2H_5\end{array} \rightarrow RCH(COOH)CH_2.COCH_3 \rightarrow \begin{array}{l}R.CH.CH{=}CCH_3\\ \quad\;\; | \qquad\quad\; |\\ \quad\; CO\text{———}O\end{array}}$$

Benzalmalonic methyl ester reacts similarly with potassium cyanide forming the compound[31] $\mathrm{C_6H_5CH(CN).CH.(COOCH_3)_2}$.

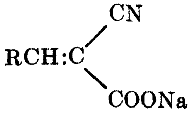
Potassium cyanide reacts in aqueous solution with benzalmalonic ester to form potassium-β-phenyl-β-cyanopropionate[35]:

$$\mathrm{C_6H_5CH{:}C(COOC_2H_5)_2 + 2KCN + 3H_2O \rightarrow C_6H_5CH(CN).CH_2COOK + HCN + KHCO_3 + 2C_2H_5OH}$$

In aqueous solution, potassium cyanide also reacts with *alkylidene-* and *arylidenecyanoacetates* to form substituted carboxysuccinonitriles, which on hydrolysis yield substituted succinic acids[32]:

$$\mathrm{RCH{:}C(CN).COONa + KCN + H_2O \rightarrow RCH(CN).CH.(CN).COONa + KOH}$$

Hydroxy- and methoxyphenylsuccinic acids have been prepared by this reaction, starting with condensation products of sodium cyanoacetate and various aromatic aldehydes,



$$\mathrm{RCH{:}C\begin{array}{l}\diagup CN\\ \diagdown COONa\end{array}}$$

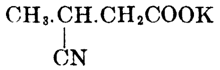
The following were prepared by Dave and Nargund[37]:

Methyl and ethyl *o*-hydroxyphenylsuccinate, m.p. 98–99°; 75°, respectively.
α-Cyano-β-*o*-methoxyphenylacrylic acid, m.p. 178°
α-Cyano-β-*m*-hydroxyphenylsuccinic acid, m.p. 124°
α-Cyano-β-*m*-hydroxyphenylacrylic acid, m.p. 170°
m-Methoxyphenylsuccinic acid, m.p. 176°
p-Aminophenylsuccinic acid, m.p. 226°
α-Cyano-β-*p*-hydroxyphenylacrylic acid, m.p. 224°
p-Hydroxyphenylsuccinic acid, m.p. 164°

In the case of benzylidenecyanoacetic acid, a further reaction occurs between a molecule of the α-cyanocinnamic acid formed and unreacted benzylidenecyanoacetic acid resulting in the formation of the compound, $C_{20}H_{17}O_2N_3$, which on boiling is converted to[33] $C_6H_5CH(CN).CH(CN).CH(C_6H_5).CH_2CN$. Ethyl benzylideneacetoacetate reacts in the same manner as benzylidenecyanoacetate[29].

Sandelin[36] prepared β-fur-β-cyanopropionic acid, $C_4H_3O.CH(CN).CH_2.COOH$, by this method from furfurylidenemalonic ester.

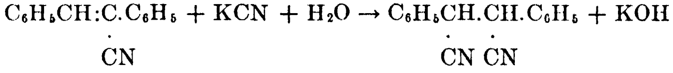
Similar reactions take place with diethyl ethylidenemalonate, $CH_3CH{:}C(COOC_2H_5)_2$, and with diethyl cinnamylidenemalonate, $C_6H_5CH{:}CH.CH{:}C(COOC_2H_5)_2$, forming, respectively, potassium β-cyanobutyrate,



$$CH_3.\underset{\displaystyle CN}{\underset{|}{C}}H.CH_2COOK$$

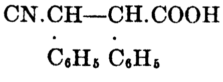
and the potassium salt of 3-cyano-6-phenyl-4-hexene-1-acid, $C_6H_5CH{:}CH.CH(CN).CH_2COOK$.

α-Phenylcinnamonitrile reacts with aqueous potassium cyanide in a similar manner to form diphenylsuccinonitrile:



$$C_6H_5CH{:}\underset{\displaystyle CN}{\underset{\cdot}{C}}.C_6H_5 + KCN + H_2O \rightarrow C_6H_5\underset{\displaystyle CN}{\underset{\cdot}{C}}H.\underset{\displaystyle CN}{\underset{\cdot}{C}}H.C_6H_5 + KOH$$

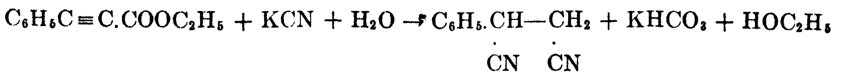
Simultaneously, a compound of the empirical formula $C_{16}H_{13}O_2N$, is formed which is probably diphenylsuccinic mononitrile[38]:



$$CN.\underset{\displaystyle C_6H_5}{\underset{\cdot}{C}}H—\underset{\displaystyle C_6H_5}{\underset{\cdot}{C}}H.COOH$$

It has been claimed that potassium cyanide reacts with *mesityl oxide* in aqueous solution to form several products depending on the concentration of reactants and the temperature[34]. Mesitonitrile, $CH_3C(CH_3)(CN).CH_2COCH_3$, is first formed but reacts rapidly to form mesitonitrile cyanohydrin, $CH_3C(CH_3)(CN).CH_2C(CH_3)(CN).OH$.

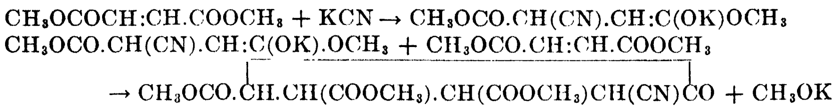
Potassium cyanide reacts in warm alcoholic solution with the ethyl ester of *phenylpropiolic acid* to form monophenylsuccinonitrile[39]:



$$C_6H_5C{\equiv}C.COOC_2H_5 + KCN + H_2O \rightarrow C_6H_5.\underset{\displaystyle CN}{\underset{\cdot}{C}}H—\underset{\displaystyle CN}{\underset{\cdot}{C}}H_2 + KHCO_3 + HOC_2H_5$$

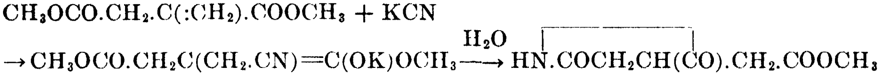
Michael and Weiner[31] showed that the reaction takes place in two steps, the first product being $C_6H_5C(CN){:}C{:}C(OK)OR$ and the final product a potassium compound of the nitrile: $C_6H_5C({:}CNK).C(COOR){:}CNK$.

Potassium cyanide reacts with *methyl fumarate* to form a 1,4 addition product which condenses with a molecule of fumaric ester to form a cyclopentanone derivative[31]:



$$CH_3OCOCH{:}CH.COOCH_3 + KCN \rightarrow CH_3OCO.CH(CN).CH{:}C(OK)OCH_3$$
$$CH_3OCO.CH(CN).CH{:}C(OK).OCH_3 + CH_3OCO.CH{:}CH.COOCH_3$$
$$\rightarrow CH_3OCO.\overset{|}{C}H.CH(COOCH_3).CH(COOCH_3)CH(CN)\overset{|}{C}O + CH_3OK$$

With methyl citraconate the first phase of the reaction involves a rearrangement to itaconic ester, which undergoes 1,4 addition and finally forms by hydrolysis a cyclic nitrogen compound as follows[31]:



$$CH_3OCO.CH_2.C({:}CH_2).COOCH_3 + KCN$$
$$\rightarrow CH_3OCO.CH_2C(CH_2.CN){=}C(OK)OCH_3 \xrightarrow{H_2O} H\overset{|}{N}.COCH_2CH(\overset{|}{C}O).CH_2.COOCH_3$$

Potassium cyanide reacts with *allyl cyanide* to form pyrotartaric dinitrile. The reaction involves the rearrangement of allyl cyanide to crotononitrile.

Potassium cyanide gives with ω-nitrostyrene an unstable addition compound, which on further reaction yields ω,ω-dinitro-α,β-diphenyl-β-cyanobutate, existing in two isomeric forms[40].

Pararosaniline salts, such as $(H_2NC_6H_4)_2{:}C{:}C_6H_4{:}NH.HCl$, digested with an alcoholic solution of potassium cyanide give the colorless hydrocyanopararosaniline[41], $(H_3NC_6H_2)_2C(CN).C_6H_4NH_2$.

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Chapter 12

Gattermann's Synthesis

Gattermann discovered that in the presence of aluminum chloride and hydrochloric acid, hydrocyanic acid reacts with certain aromatic compounds to form what he thought to be a simple aldimine. On hydrolysis with acids, the initial addition product forms an aromatic aldehyde[1]. The original assumption that in this reaction a simple aldimine, RCH=NH is first formed appears to be untenable, and from the work of L. E. Hinkel and his co-workers[2], it would appear that, in the presence of aluminum chloride, methyleneformamidine hydrochloride is first formed. These authors have shown that the double compound, $AlCl_3.2HCN$, which also forms when hydrocyanic acid is brought into contact with aluminum chloride, combines with hydrochloric acid at 80°, giving: $AlCl_3.2HCN.HCl$, identical with the product of reaction of aluminum chloride and chloromethyleneformamidine, HN:CH.N:CH.Cl. The reaction with benzene may thus be represented as follows:

$$C_6H_5 + AlCl_3.NH:CH.N:CH.Cl \rightarrow C_6H_5.CH:N.CH:NH.HCl + AlCl_3$$

The phenylchloromethyleneformamidine is hydrolyzed with hydrochloric acid to benzaldehyde:

$$C_6H_5.CH:N.CH:NH.HCl + 3H_2O \rightarrow C_6H_5.CHO + NH_4OCOH + NH_4Cl$$

Hinkel *et al.*[3] have shown that chloromethyleneformamidine, NH:CH.N:-CHCl, combines with resorcinol to form resorcylmethyleneformamidine hydrochloride in 90% yield, and this on hydrolysis gives resorcylaldehyde. Resorcinol reacts with hydrocyanic acid in the presence of hydrogen chloride to form the resorcinol aldimine product[4]:

$$C_6H_4(OH)_2 + 2HCN + HCl \rightarrow C_6H_3.(OH)_2.CH:N.CH:NH.HCl$$

Gattermann prepared a large number of aromatic aldehydes by his method He obtained *p*-hydroxyaldehydes from *phenol, o-* and *m-cresol, o-ethylphenol p-xylenol, 2,3-dimethylphenol, 1,6-dimethylphenol, 3,5-dimethylphenol, thymol, carvacrol, α-naphthol, tetrahydro-α-naphthol;* the yields of aldehyde ranging from 50 to 90% of theory. *β-Naphthol* gave an *o*-aldehyde.

Resorcinol, orcinol and cresorcinol gave aldehydes in which the formyl group occupied the free *p*-position with respect to an OH; *1,5-dihydroxynaphthalene* gave *1,5-dihydroxy-4-formylnaphthalene, 2,7-dihydroxynaphthalene* gave 1-formyl-2,7-dihydroxynaphthalene, and the *2,6-hydroxy* compound gave 1-formyl-2,6-dihydroxynaphthalene.

The formyl group occupied the *p*-position with respect to the uncombined hydroxy group in the monomethyl esters of resorcinol and orcinol.

The reaction proceeded well with the esters of monohydric phenols, including the compounds: $C_6H_5OCH_2CH_2Br$ and (o)$CH_3.C_6H_4.OCH_2CH_2Br$.

The neutral ethers of dihydric phenols behaved in the same way as the mother substances. *Hydroquinone dimethyl* ether gave 1,4-dimethoxy-3-formylbenzene.

Ethers of monohydric phenols with ethylene glycol or other dihydric alcohols, such as: $C_6H_5OCH_2CH_2O.C_6H_5$, also give aldehydes in which the aldehyde grouping occupies the *para* position with respect to the alkoxy group. *Bis-α-naphtholtrimethylene ether* gives: (4)-$OCH.C_{10}H_6.OCH_2CH_2CH_2O.C_{10}H_6$-CHO-(4′). The *β-naphthol ether* gives: (1)-$OCHC_{10}H_6OCH_2CH_2CH_2OC_{10}H_6$-CHO-(1′). The neutral ethers of *o*-dihydroxydiphenyl give dialdehydes in which the formyl groups occupy the *para* position with respect to the alkoxy groups[5]. Of the monomethoxydiphenyl ethers, the 2-methoxy isomer gives a mixture in approximately equal amounts of 5- and 4′-aldehydes; the 3-methoxy isomer gives 4- and 6-aldehydes, the former predominating[6].

Gattermann failed to convert *benzene* to benzaldehyde, and Houben and Fischer, and later Wieland and Dorrer, on their part, arrived at the conclusion that the Gattermann synthesis was not applicable to aromatic hydrocarbons[7].*

Hinkel and co-workers[8] demonstrated, however, that the synthesis may be successfully carried out in an excess of the hydrocarbon as a solvent or in another suitable solvent, at the proper temperature. They describe their procedure as follows:

> Powdered aluminum chloride was suspended in the solvent and hydrogen cyanide was added slowly during fifteen minutes, the reaction vessel being shaken and cooled. The mixture was kept at room temperature for fifteen minutes with frequent shaking. The requisite hydrocarbon was then added, and a slow current of hydrogen chloride was passed through the mixture for fifteen minutes at room temperature. The mixture was next heated in a water bath at the chosen temperature and for the required period of time, the passage of hydrochloric acid being continued, and the mixture being shaken at ten-minute intervals. The dark, viscous product was then poured into a mixture of ice and concentrated hydrochloric acid, and the whole was heated to boiling for fifteen minutes. The aldehyde was then isolated.

Hinkel and co-workers[8] prepared the following aldehydes from the corresponding hydrocarbons:

2,4,6-Trimethylbenzaldehyde, b.p. 236–237°
|Mixed ethylbenzaldehydes
Diphenyl-4-aldehyde, b.p. 80–100°, m.p. 60°
α-Naphthaldehyde, b.p. 291–292°
1-Methyl-4-naphthaldehyde, b.p.$_{11}$ 171°
1,6-Dimethyl-4-naphthaldehyde, b.p.$_{16}$ 191.5°
2,6-Dimethyl-1-naphthaldehyde, m.p. 57°
1,2,3,4-Tetrahydro-6-naphthaldehyde, b.p.$_{14}$ 138
Hydrindene-5-aldehyde, b.p. 255–257°
Anthracene-9-aldehyde, m.p. 104–105°

* Prior to Gattermann's publication Bayer and Company described the preparation of aldehydes from aromatic hydrocarbons by this method, though failing to mention specifically the formation of benzaldehyde from benzene (*German Patent* 99,568).

Phenanthrene-9-aldehyde, b.p. 231–233°
Acenaphthene-3-aldehyde, m.p. 87°
Fluorene-2-aldehyde, m.p. 90°
Diphenyl-4,4′-dialdehyde, m.p. 145°

The yields ranged from about 44% to as much as 83% of the theoretical, except in the case of 1,2,3,4-tetrahydro-6-naphthaldehyde (4%), diphenyl-4,4′-dialdehyde (13%) and mixed ethylbenzaldehydes (22.4%)[8].

These authors failed to obtain *dialdehydes* except with *diphenyl*, which yielded 4,4′-diphenylaldehyde, the aldimine groups entering the molecule simultaneously. The solvent had a marked influence on the course of the reaction; thus, when chlorobenzene or *o*-dichlorobenzene was used as a solvent, only the monoaldehyde formed, whereas in trichloroethane the dialdehyde alone formed. 2,4,6-Trimethyl-3-hydroxybenzaldehyde, 2,3-dimethyl-4-hydroxybenzaldehyde and 3,4,5-trimethyl-2-hydroxybenzaldehyde have been obtained from the methyl ester of mesitol, *o*-xylenol and helmitol respectively by the same method[48].

Success in this reaction is dependent upon the presence of free aluminum chloride above the quantity required for the formation of the compound: $AlCl_3$.-2HCN. When the quantity of aluminum chloride present is just sufficient to form this compound, no aldimine is formed. The yield increases up to a maximum, with increase in the amount of excess aluminum chloride. Thus, in the case of toluene, *p*-tolualdehyde is obtained in yields of 23, 31 and 39% of theory, respectively, with 0.5, 1 and 2 moles of aluminum chloride in excess. The solvent plays an important role; thus, *p*-methoxybenzaldehyde forms in yields ranging up to 50% of theory from anisole in the absence of other solvents, or in ethylbenzene, but the reaction does not proceed in carbon disulfide, carbon tetrachloride, nitrobenzene or cyclohexane.

Sodium cyanide may be used in the reaction in place of hydrocyanic acid. Through a suspension of sodium cyanide and aluminum chloride in the hydrocarbon maintained at room temperature, a slow current of dry hydrogen chloride is passed for fifteen minutes; the mass is then gradually heated to 100° and the passage of hydrogen chloride is continued for seven hours at this temperature. By this method, Niedzielski and Nord[9] prepared tolualdehyde, 3,4-dimethylbenzaldehyde and di*iso*propylbenzaldehyde from the corresponding hydrocarbons in 39, 42 and 18% yield, respectively. The reaction has been successfully carried out also with zinc cyanide and hydrochloric acid in the presence of aluminum chloride[45]. Pure zinc cyanide does not show catalytic activity in the Gattermann synthesis but zinc cyanide to which a small amount of sodium chloride has been added is an active catalyst[10].

Directive Influence of Substituents

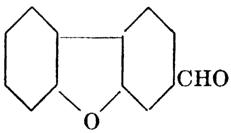
Substituents in the aromatic ring other than chlorine, hydroxy or alkoxy groups, retard or completely inhibit the reaction. The *nitro*, *carboxy*, *amino*, *azo*, *acetyl* groups and *quinoid oxygen* exert a particularly strong inhibitive influence. 2-Hydroxy-, 2-methoxy-, and 2,2′-dihydroxydiphenyl do not yield aldehydes by the Gattermann method[11]. Phenol ethers give better yield of aldehydes, but the reaction takes place less readily with these compounds.

Alkoxy groups exert a *para* directing influence. When two such groups are present, the directive influence is shared by both. The directive influence of the groups allyl, ethyl, *n*-propyl, benzyl and methoxy increases in the order named[12].

Sonn and Patschke[12] prepared the following compounds:

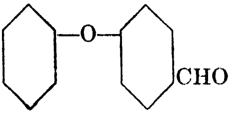
	M.P.	*Total Yield,* *%*	*Proportion,* *%*
2-Methoxy-4-ethoxy-1-benzaldehyde	58–59	57	55
2-Ethoxy-4-methoxy-1-benzaldehyde	64–65		45
2-Methoxy-4-propyloxy-1-benzaldehyde	45	52	50
2-Propyloxy-4-methoxy-1-benzaldehyde	37		50
2-Methoxy-4-allyl-1-benzaldehyde	47–48	51	70
2-Allyl-4-methoxy-1-benzaldehyde	38		30
2-Methoxy-4-benzyloxy-1-benzaldehyde	95	40	49
2-Benzyloxy-4-methoxy-1-benzaldehyde	67		51

Aldehydes have been obtained from *pyrrole, thiophene, furane* and *diphenyloxide.* Pyrrole is more reactive than furane and the latter, in turn, reacts more readily than thiophene. All three form 2-carbonyl derivatives[13]. Hinkel and co-workers[14] prepared dibenzfurane-3-aldehyde,



(m.p. 68°)

Diphenyloxide forms a 4-carbonyl compound,



in good yield[15].

Phenol reacts with hydrocyanic acid at 40° in the presence of aluminum chloride and hydrogen chloride presumably to form *p*-hydroxyphenylchloromethylene formamidine hydrochloride from which *p*-hydroxybenzaldehyde is obtained by hydrolysis[16]. *Anisaldehyde* may be obtained in a similar manner from anisol[17]. 4-Phenoxybenzaldehyde has been obtained in 70 to 80% yield by this reaction from *diphenyloxide,* using 30 to 50% excess of hydrocyanic acid over the theoretically required quantity[18].

Of the three dihydroxybenzenes, only one, namely resorcinol, undergoes the Gattermann condensation. *Resorcinol* reacts readily with hydrocyanic acid in ether solution saturated with hydrogen chloride in the absence of aluminum chloride to form 2,6-dihydroxybenzaldimine hydrochloride, from which the aldehyde may be obtained by hydrolysis[19].

The following aldehydes were prepared by condensation of the appropriate phenolic compound with hydrocyanic acid in the presence of zinc cyanide and hydrochloric acid and subsequent hydrolysis of the addition product formed[46]:

	M.P. °*C*
2-Hydroxy-4-methoxy-5-ethoxybenzaldehyde	112–113
2-Hydroxy-4,5-dimethoxybenzaldehyde	105
2,5-Dihydroxy-4-methoxybenzaldehyde	209
2-Hydroxy-5-methoxy-4-ethoxybenzaldehyde	91

Substituted resorcinols also form aldimine compounds, the aldimine group entering the *ortho* position with respect to both hydroxy groups unless this position is already occupied with a substituent. Shah and co-workers have prepared several aldehydes from substituted resorcinols, by the use of zinc cyanide as a catalyst in ethereal solution:

2,6-Dihydroxy-3,5-dimethylbenzaldehyde[20]
2,4-Dihydroxy acetophenone-3-aldehyde
2,4-Dihydroxy-6-methyl acetophenone-3-aldehyde [21]
2,6-Dihydroxy acetophenone-5-aldehyde
2,4-Dihydroxy benzophenone-3-aldehyde
Methyl-2,4-dihydroxy-3-formyl-5-ethylbenzoate[22]
2,4-Dihydroxy-3-formylacetophenone[23]
2,4-Dihydroxy-3-formyl-5-ethylacetophenone
2,4-Dihydroxy-3-formyl-6-methylacetophenone [24]
2,6-Dihydroxy-3-formylacetophenone
2,4-Dihydroxy-3-formylpropiophenone
2,4-Dihydroxy-3-formyl butyrophenone [25]
2,4-Dihydroxy-3-formylbenzophenone
2,4-Dihydroxy-3-formylphenyl benzyl ketone
2-Hydroxy-4,6-dimethoxy-5-methylbenzaldehyde (m.p. 85°)
2,4-Dihydroxy-6-ethoxybenzaldehyde (m.p. 169°) [26]
2,6-Dihydroxy-4-ethoxy-3-methylbenzaldehyde (m.p. 196–197°)

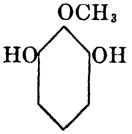
Karrer and co-workers[27] prepared the following:

2,3-Dimethyl-5-hydroxycoumarone-4-aldehyde m.p. 210°
Phlorglucinolmonomethyl ether aldehyde m.p. 203°

Späth and Gruber prepared[28]:

C-Ethylphlorglucinol aldehyde, m.p. 174–6°, in 78% yield.

2,4-Dihydroxy-3-methoxybenzaldehyde is obtained from the *monomethyl ether of pyrogallol*,



by reaction with hydrocyanic acid in ether solution in the presence of zinc cyanide and excess hydrogen chloride and subsequent hydrolysis[29]. Under the same conditions, *trimethylhydroquinone* forms, in 47% yield, 2,5-dihydroxy-3,4,6-trimethylbenzaldehyde; a yellow compound melting at 146–7°[30].

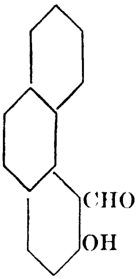
Resorcinol dimethyl ether in ether solution gives the 2:4-dimethoxy aldimine compound from which 2,4-dimethoxybenzaldehyde may be obtained by hydrolysis.

2-Hydroxy-1-naphthaldehyde has been obtained from *β-naphthol*[31].

Morgan and Vining[32] have applied the Gattermann synthesis to *dihydroxynaphthalenes* and have prepared the following in the yields indicated:

	M.P. °C	*Yield, %*
3,4-Dihydroxy-1-naphthaldehyde	190–200	21
2,3-Dihydroxy-1-naphthaldehyde	133.5–134.5	62
2,4-Dihydroxy-1-naphthaldehyde	214	42
1,4-Dihydroxy-2-naphthaldehyde	188–190	13
2,6-Dihydroxy-1-naphthaldehyde	189–190	
2,7-Dihydroxy-1-naphthaldehyde	156.5–158.5	70
4,8-Dihydroxy-1-naphthaldehyde		
4,5-Dihydroxy-1-naphthaldehyde	150–160	24
4,7-Dihydroxy-1-naphthaldehyde	dec. 218	64
2,5-Dihydroxy-1-naphthaldehyde	225–230	12–20
4,6-Dihydroxy-1-naphthaldehyde	265–270	
2,8-Dihydroxy-1-naphthaldehyde	203–204 dec.	

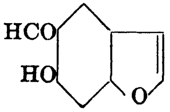
3-Phenanthrol-4-aldehyde,



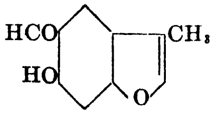
has been prepared from *3-phenanthrol* by the Gattermann reaction[33].

Aldehydes have been prepared by the Gattermann method from various *methylfuranes*[34]. The formyl group always enters the 2-position. *3-Methylfurane* gives 2-formyl-3-methylfurane; *2-methylfurane* forms 2-methyl-5-formylfurane; 2,4-methylfurane gives 2,4-methyl-5-formylfurane.

6-Hydroxycoumarone, and *3-methyl-6-hydroxycoumarone* give respectively 5-formyl-6-hydroxycoumarone,

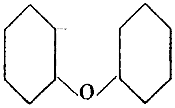


and 3-methyl-5-formyl-6-hydroxycoumarone[35],



4,6-Dimethoxy-2-carbethoxycoumarone and *4-methoxy-6-hydroxy-2-carbethoxy-coumarone* form 7-formyl compounds[36].

Dibenzfurane-3-aldehyde (m.p. 68°) has been obtained in 81% yield from *dibenzfurane*,

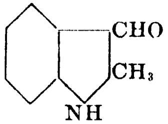


by the Gattermann reaction using aluminum chloride as a catalyst and tetrachloroethane as a solvent, and heating for five hours at 80°[37].

3,4-Dimethylpyrrole forms 3,4-dimethylpyrrole-2-aldehyde[38]. *2,4,5-Trimethylpyrrole* gives 2,4,5-trimethylpyrrole-3-aldehyde in 66% yield when chloroform is used as a solvent reaction failing to take place in ether solution[39]. *2,4-dimethyl-3-carbethoxypyrrole* and *2,5-dimethoxy-3-carbethoxypyrrole* form the 5- and 4-aldehydes in 95% and 76.5% yield, respectively, in ether solution[40]. 2-Phenyl-5-pyrrole aldehyde has been obtained from 2-phenylpyrrole[49].

Gatterman's synthesis has been applied to *aniline*, the reaction product giving upon hydrolysis *p*-aminobenzaldehyde[47].

3-Methyl-3-formylindole,



may be obtained from *2-methylindole* in ether solution without the use of a catalyst[41].

Indole-3-aldehyde-2-carboxylic acid has been prepared from indole-2-carboxylic ester through reaction with zinc cyanide and hydrochloric acid[50].

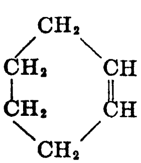
Application of Gattermann's Synthesis to Unsaturated Compounds

Wieland and Dorrer[42,44] applied the Gattermann synthesis to unsaturated compounds, and in particular to enols. Since unsaturated compounds form a variety of condensation products in the presence of aluminum chloride, the Gattermann synthesis may be successfully carried out only in isolated cases. Thus, *diphenylethylene* condenses with hydrocyanic acid in the presence of aluminum chloride to form α,α-diphenylpropionitrile:

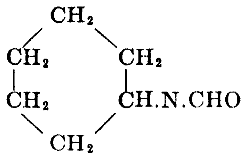
$$(C_6H_5)_2C{:}CH_2 + HCN \rightarrow (C_6H_5)_2C(CN).CH_3$$

This reaction should not be confused with the usual addition of HCN to certain double bonds. The latter occurs only when a negative group such as CO or CN is attached to one of the carbon atoms forming part of the olefinic group, and the CN group of HCN attaches itself to the carbon in the β-position with respect to the CO or the CN group originally present in the molecule.

With *cyclohexene,*

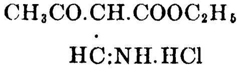


a different type of reaction takes place and the final product obtained is N-formylcyclohexylamine,



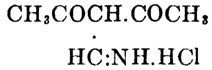
which forms in 30% yield[43].

Wieland and Dorrer[44] showed that enolic forms of certain ketones react with hydrocyanic acid in the presence of aluminum chloride to form what they regarded to be aldimines, and ascribed the formula



$$\begin{array}{c}\mathrm{CH_3CO.\dot{C}H.COOC_2H_5}\\ \mathrm{HC{:}NH.HCl}\end{array}$$

to the compound obtained from *ethylacetoacetate* and



$$\begin{array}{c}\mathrm{CH_3CO\dot{C}H.COCH_3}\\ \mathrm{HC{:}NH.HCl}\end{array}$$

to that obtained from *acetylacetone.*

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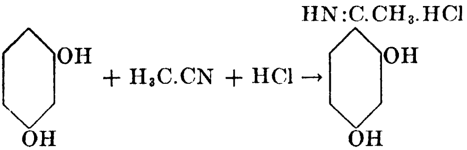
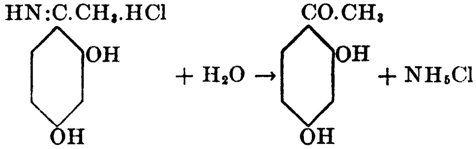
Chapter 13

Houben-Hoesch Synthesis

The Houben-Hoesch synthesis* is the extension of the Gattermann synthesis to nitriles in general. Hydroxy compounds react normally with nitriles in the presence of hydrogen chloride to form iminoethers. While the normal reaction leading to the formation of iminoethers occurs in most cases, in many others the CN-group adds on to a nuclear carbon atom forming a ketimine:



The ketimine may be readily hydrolyzed to the corresponding ketone:



This, in essence is the Hoesch synthesis. In the majority of cases, the reaction proceeds only in the presence of catalysts, such as zinc chloride or aluminum chloride.†

The importance of the Houben-Hoesch synthesis is shown by the fact that up to the year 1929 the following natural products were prepared by its use[2]: Peonol, *iso*peonol, maclurin, phloretin, *iso*naringin, *iso*aspidinol, *iso*cotoin, aspidinol, *pseudo*-aspidinol, aromadindrin, fisetol, gatangin, campherid, resocampherid, resogalangin, *iso*rhamnetin, *i*-brasilein derivative, fisetin, quercetin, galangin monomethyl ester, myricetin, protocotoin, *iso*protocotoin, cotogenin, methylprotocotoin, morin, syringetin, gossypetin and quercetagetin. The following anthelmintics were also made: Trihydroxybutyro- and *iso*butyrophenon, methyl trihydroxybutyro- and *iso*butyrophenon, dimethyl trihydroxybutyro- and *iso*butyrophenone, res*iso*- and phlor*iso*-caprophenone, phlorophenylacetophenone. In addition, the following anti-diarrheals were prepared *iso*cotoin, 2,4,6,2-, 2,4,6,4′-, 2,3,4,2′-, 2,4,2′,4′-tetrahydroxybenzophenone, 2,4,2′-trihydroxybenzophenone, 2,3,4,2′,4′-pentahydroxybenzophenone, 3-hydroxyxanthon, 3,4-dihydroxyxanthon, 3,6-dihydroxyxanthon.

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* Before Hoesch s discovery of this reaction Minovici[1] investigated the reaction between resorcinol and benzaldehyde cyanohydrin in the presence of hydrogen chloride, and thus carried out a reaction in the sense of the Hoesch synthesis, but he failed to recognize the true nature of the reaction product.

† Nitriles give double compounds with aluminum chloride. Perrier[27] identified the following: $4HCN.2AlCl_3$, $2HCN.2AlCl_3$, $4CH_3CN.2AlCl_3$, $2CH_3CN.2AlCl_3$, $CH_3CN.2AlCl_3$, $4C_2H_5CN.2AlCl_3$, $2C_2H_5CN.2AlCl_3$, $C_2H_5CN.2AlCl_3$, $4C_6H_5CN.2AlCl_3$, $2C_6H_5CN.2AlCl_3$ $C_6H_5CN.2AlCl_3$. Genvresse[40] prepared $ClCH_2CN.2AlCl_3$ and $Cl_3CCN.2AlCl_3$.

The Effect of Substituents in the Aromatic Ring

The Houben-Hoesch reaction proceeds most readily in the case of resorcinol and other *meta*-dihydroxyphenols and with phlorglucinol. The alkyl ethers of these phenolic compounds, in general, also from ketimines with nitriles.

Halogens in the *ortho* position with respect to a hydroxyl or alkoxy group, greatly hinder the reaction. On the other hand, a *methyl* group in the *ortho* position favors the reaction. A methyl group in the *meta* position causes some decrease in the reaction velocity, and one in the *para* position greatly hinders the reaction. a *nitro* group in the *ortho* position almost completely inhibits the reaction. A *carboxyl* group in the *ortho* position reacts preferentially with the nitrile group to form an acyl imine: $R_1CO.N:CCl.R_2$. The *hydroxyl* group exerts a *para* directing influence; the directing action of the *methoxy* group is as strong as that of the hydroxyl group.

The solvent has a decided influence on the velocity of reaction, the reaction taking place most readily in ether and, in general, only very slowly in most other solvents[3].

Example of Procedure. As an example of the procedure the method followed by Hoesch for the preparation of resacetophenone is given below:

Five grams of resorcinol and 3 of acetonitrile are dissolved in 25 cc of anhydrous ether and 2 grams of pulverized, anhydrous zinc chloride are added. A stream of dry hydrogen chloride is then passed through the solution for about half an hour. The vessel is stoppered and allowed to stand a few hours. The solution is then cooled and 25 cc of water are added. The main portion of the resacetophenone formed is extracted with ether, and the aqueous solution is heated to boiling for half an hour. Upon cooling, crystals of resacetophenone separate and are filtered. The combined yield is 70% of the theoretical.

Syntheses with Polyhydric Phenols and Their Ethers

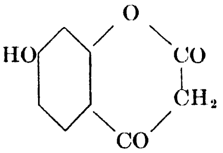
Hoesch[7] condensed *acetonitrile* and *benzonitrile* with *resorcinol*, *orcinol* and *phloroglucinol*. The melting points and yields of the carbonyl compounds obtained are given in the following table:

	M.P. °C	*Yield,* %
2,4-Dihydroxyacetophenone (Resacetophenone)	144–145	70
2,4-Dihydroxy-6-methylacetophenone (Orcacetophenone)	159	
2,4,6-Trihydroxyacetophenone (Phloracetophenone)	218	80
2,4-Dihydroxybenzophenone (Benzoresorcin)	144	40
2,4-Dihydroxy-6-methylbenzophenone (Benzoörcin)	141	
2,4,6-Trihydroxybenzophenone (Benzophlorglucin)[8]	165	65

Karrer and Rosenfeld[11] condensed resorcinol with *butyro-*, *isocapro- oenantho-* and *caprylonitrile* to obtain, upon hydrolysis of the ketimines, resorcinbutyrophenone, m.p. 70°, resorcin*iso*caprophenone m.p. 78°, resorcinoenanthophenone, m.p. 49°, resorcincaprylophenone, m.p. 59°.

Fisetol has been prepared from *resorcinol* and *glycolonitrile*[69]. Condensation products have been prepared also from resorcinol and *hippuryl cyanide*, *carbethoxyaminoacetonitrile* and *carbethoxyoxyglycolonitrile*. The final reaction products, after the hydrolysis of the ketimines first formed, are ω-(benzoylamino)-resacetophenone, m.p. 255° (dec.), ω-(carbethoxyamino)-resacetophenone, m.p. 156–157°, and ω-(carbethoxyoxy)-resacetophenone, $(HO)_2C_6H_3COCH_2OCOOC_2H_5$, m.p. 104–105°. Carbethoxyglycolonitrile has also been condensed with the dimethyl ether of resorcinol to give, after hydrolysis of the ketimine, ω-(carbethoxyoxy)-resacetophenone dimethylether, m.p. 74–75°[70].

Resorcinol, condensed with *ethyl cyanoacetate* in the presence of zinc chloride, forms a ketimine which upon hydrolysis gives 4,7-dihydroxycoumarin



A similar compound is obtained from phloroglucinol[12]. Condensation of *cyanoacetic acid* with resorcinol gives the same compound, while resorcinol and *malononitrile* give ω-cyanoacetoresorcinol, m.p. 270–272°, phloroglucinol giving similarly ω-cyanoacetophloroglucinol, m.p. 260°[71].

Resorcinol condensing with *acetoxyacetonitrile* in the presence of hydrogen chloride gives the ketimine of ω-acetoxyresacetophenone, $(HO)_2C_6H_3$-$C(:NH)CH_2OCOCH_3$, from which the ketone, melting at 164.5° is obtained on hydrolysis[58]. Condensation with *benzoyloxyacetonitrile* gives ω-benzoyloxyresacetophenone, m.p. 202–203°. Phloroglucinol similarly gives with this compound ω-benzoyloxyphloroacetophenone, m.p. 231–233°, hydrolysis of the ketimine requiring treatment with boiling 50% aqueous alcohol for twenty-one hours. 3,7-Dihydroxyflavone and *Galangin* have been made from these benzoyloxyphenones by Perkin's synthesis[72].

Resorcinol condensing with *ethylene dicyanide* in the presence of zinc powder and hydrogen chloride gives, after hydrolysis of the ketimine formed, β-(2,4-dihydroxybenzoyl)-propionic acid, $(HO)_2C_6H_3COCH_2CH_2COOH$, m.p. 199–200°[59].

γ-(2,4-Dihydroxybenzoyl)-butyric acid, m.p. 175–178°, is obtained similarly with *trimethylene dicyanide*, $CNCH_2CH_2CH_2CN$. Phloroglucinol gives with this nitrile α,γ-bis-(2,4,6-trihydroxybenzoyl)-propane, m.p. 286–286.5°, with some γ-(2,4,6-trihydroxybenzoyl)-butyric acid, m.p. 247–249°. With *tetramethylene dicyanide*, resorcinol gives α,δ-bis-(2,4-dihydroxybenzoyl)-butane, m.p. 285–288° and 2,4-dihydroxyphenyl-ω-cyanobutyl ketone, m.p. 157–159°, while phloroglucinol gives α,δ-bis-(2,4,6-trihydroxybenzoyl)-butane, dec. at 265°[60].

3-Hydroxy-5-methoxybenzonitrile has been condensed with resorcinol to give, after hydrolysis, vanillinoresorcinol in 20% yield; this nitrile as well as 3,5-dihydroxybenzonitrile have also been made to react with phloroglucinol giving as the final product vanillinophloroglucinol and maclurin in 33 and 37% yield respectively[9].

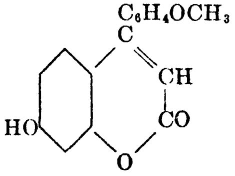
3-Hydroxyxanthone, m.p. 246°, has been obtained through the condensation of resorcinol with *o-acetoxybenzonitrile* and subsequent hydrolysis of the reaction product; 3,6-dihydroxyxanthone, m.p. > 300°, has been similarly obtained, though in an extremely small yield (1% of theory), from resorcinol and *diacetyl-β-resorcylonitrile*. Pyrogallol gives with these nitriles 2,3,4,2′-tetrahydroxybenzophenone, m.p. 149°, and 2,3,4,2′,4′-pentahydroxybenzophenone, m.p. 187°, the former in a yield of 18.5% of theory[13].

6-Bromopiperonylresacetophenone, m.p. 163°, has been obtained in 30% yield from resorcinol and *β-6-bromopiperonylpropionitrile*[14].

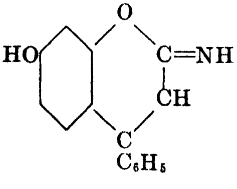
Resorcinol has been condensed with *phenylacetonitrile*, *p-chlorophenylacetonitrile* and *p-tolylacetonitrile*, the final products of hydrolysis being 2,4-dihydroxydeoxybenzoïn, m.p. 115°, 4′-chloro-2,4-dihydroxydeoxybenzoïn, m.p. 153–154°, and 2,4-dihydroxy-4′-methyldeoxybenzoïn, m.p. 114°. 2,4,6-Trihydroxydeoxybenzoïn, m.p. 162°, 4′-chloro-2,4,6-trihydroxydeoxybenzoïn, m.p. 221–222°, and 2,4,6-trihydroxy-4′-methyldeoxybenzoïn, m.p. 205–206°, have also been prepared through the condensation of these nitriles with phloroglucinol[73].

Benzylresacetophenone, $(HO)_2C_6H_3COCH_2CH_2C_6H_5$, m.p. 88°, has been prepared from resorcinol and *β-phenylpropionitrile*, and benzylphloroacetophonone, m.p. 139–140° and benzylorcacetophenone, m.p. 118.5°, from this nitrile and phloroglucinol and orcinol[74].

2-Ketonitriles behave in an abnormal manner, yielding upon hydrolysis of the addition products, coumarin derivatives. Thus, the reaction product of resorcinol and *p-methoxybenzoylacetonitrile*, $CNCH_2COC_6H_4OCH_3$, gives on hydrolysis 7-hydroxy-4-*p*-methoxyphenylcoumarin[75],

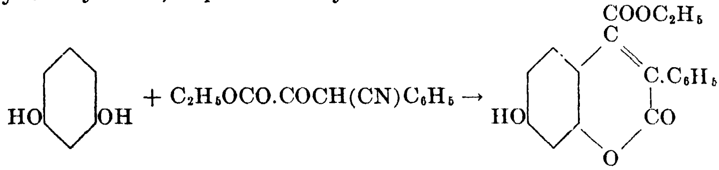


Sonn[15] showed that *benzacetodinitrile*, $C_6H_5C(:NH)CH_2CN$, reacting with resorcinol in the presence of hydrogen chloride, yields the ketimine of 7-hydroxy-4-phenylcoumarin,



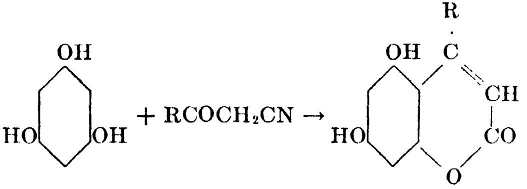
and not, as Meyer believed, that of 3-hydroxyflavone[15]. This behavior is to be expected since the dinitrile is related to benzoylacetonitrile, and it may indeed be assumed that the ketonitrile is formed as the first step in the reaction.

Ethyl phenylcyanopyruvate reacts in this abnormal manner, the product of the reaction with resorcinol, after hydrolysis, being 3-phenyl-7-hydroxycoumarin-4-carboxylic ethyl ester, m.p. of monohydrate 190–191°:

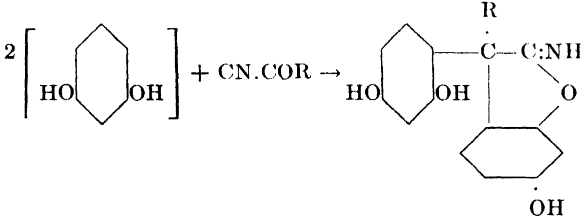


Condensation has been brought about in glacial acetic acid in the presence of aluminum chloride. Methyl-3-phenyl-6-hydroxycoumarin-4-carboxylic ethyl ester and 3-phenyl-5,7-dihydroxycoumarin-4-carboxylic ethyl ester have also been prepared from orcinol and phloroglucinol[18].*

Cyanobenzophenone and substituted cyanobenzophenones react similarly with phlorglucinol to form the ketimine of phenylcoumarin derivatives, from which the corresponding coumarin is obtained by hydrolysis[19]:



Marsh and Stephen[20] condensed *arylglyoxylic nitriles* with resorcinol by the Hoesch method. Borsche and Walter[21] showed that the condensation takes place in the following manner:



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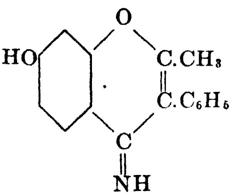
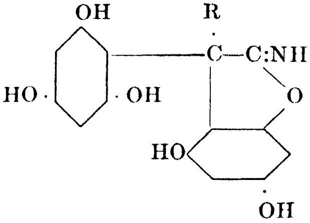
* Ghosh prepared a large number of condensation products from nitriles of the type $C_1H_1CH(COR)CN$ with resorcinol and other aromatic hydroxy compounds and assumed these to be benzopyran derivatives such as



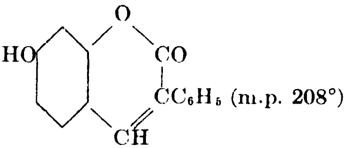
without, however, offering proof other than the correspondance of the analytical result with values expected on this assumption.[76]

Phloroglucinol reacts in a similar manner to form compounds of the type



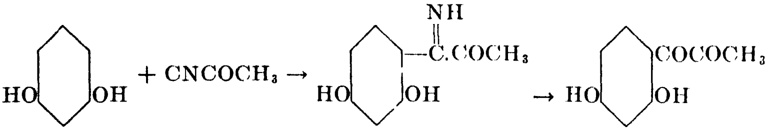
Compounds of this type in which R was C_6H_5—, p-ClC_6H_4— p-$CH_3OC_6H_4$— have been prepared[22].

α-Formylphenylacetonitrile, $OCH.CH(C_6H_5)CN$, reacting with resorcinol in the presence of zinc chloride gives, after hydrolysis, 7-hydroxy-3-phenylcoumarin,



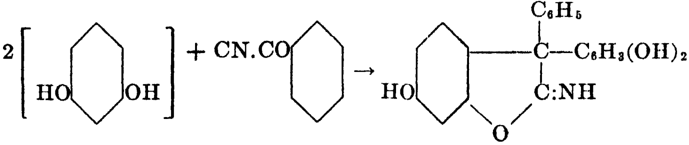
the monomethyl ether of resorcinol gives 7-methoxy-3-phenylcoumarin, m.p. 121–122°. Phlorglucinol gives 5,7-dihydroxy-3-phenylcoumarin, m.p. 260°. Similarly 5,7-dimethoxy-3-(4′-methoxyphenyl)-coumarin, m.p. 166–168° has been made from the dimethyl ether of phlorglucinol and *α-formyl-p-methoxyphenylacetonitrile;* 5,6,7-trimethoxy-3-(3′,4′,5′-trimethoxyphenyl)-coumarin, m.p. 157°, from *α-formyl-3,4,5-trimethoxyphenylacetonitrile* and 3,4,5-trimethoxyphenol[62].

Alkylglyoxylic nitriles react normally with resorcinol to form ketimines, from which the corresponding 1,2-diketones may be readily obtained by hydrolysis:



By this reaction, derivatives from propionyl cyanides have also been prepared, as well as the corresponding compounds from phloroglucinol[16].

Aryl glyoxylic nitriles, on the other hand, react with polyhydroxy aromatic compounds to form polyhydroxyphenylacetic lactimines, from which the corresponding lactones form by hydrolysis[17]:

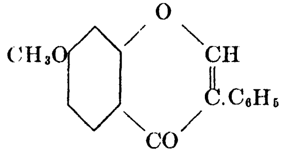


1-Methyl-2,6-dihydroxyphenol has been condensed with *propio-*, *butyro-* and *phenylacetonitrile* giving upon hydrolysis of the intermediate ketimine, 2,4-

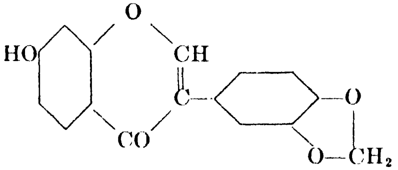
dihydroxy-3-methylpropiophenone, m.p. 128–130 (yield 50%), 2,4-dihydroxy-3-methylbutyrophenone, m.p. 155–157° and 2,6-dihydroxy-*m*-tolyl benzyl ketone respectively[10].

Resorcinol dimethyl ether has been condensed with *formaldehyde cyanohydrin* to hydroxymethyl-2,3-dimethoxyphenylketimine[26], $(CH_3O)_2C_6H_3C(=NH).CH_2OH$.

Robinson prepared the monomethyl ether of resorcinolacetophenone cyanohydrin, from which he obtained by Hoesch's synthesis and subsequent dehydration of the ketone, the *iso*flavone



In a similar manner, Spath and Lederer[28] prepared *pseudo*paptigenin,



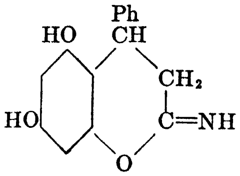
Isovalero-, *isobutyro-*, *isocapro-*, *oenantho-*, *caprylo-* and *stearonitriles* have been condensed with *phloroglucinol* to yield the corresponding phlorophenones; *iso*carpo-, oenantho- and caprylonitrile have also been condensed with methylphloroglucinol to the corresponding phenones[11]. *Butyronitrile* has also been condensed with phloroglucinol to yield phlorobutyrophenone, as well as with methylphloroglucinol, dimethylphloroglucinol and the methyl ether of phloroglucinol giving the corresponding phenones[30].

Malononitrile has been condensed with phloroglucinol to a monoketimino compound, $(HO)_3C_6H_2C(:NH).CH_2CN$, a small quantity of the diketimine, $[(HO)_3C_6H_2C(:NH)]_2CH_2$, also forming. Both may be hydrolyzed to the corresponding keto compound[12]. Phlorobenzophenone and phloroglucinolmethoxy acetophenone have been obtained from phloroglucinol and *benzonitrile* and *methoxyacetonitrile* respectively[26]. 2,4,6,2′-Tetrahydroxybenzophenone has been prepared from phloroglucinol and *salicylonitrile*.

p-Nitrobenzyl cyanide reacting with phloroglucinol in the presence of zinc chloride gives, after hydrolysis of the ketimine first formed, 4-nitrobenzyl 2,4,6-trihydroxyphenyl ketone, m.p. 270°. The corresponding 2- and 3-nitrobenzyl analogs have also been prepared from *o*- and *m*- nitrobenzyl cyanides[61].

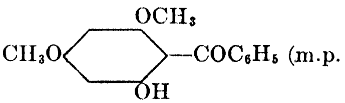
Phloretin, $(HO)_3C_6H_2COCH_2CH_2C_6H_4OH(p)$, m.p. 262–264°, has been prepared from *phloroglucinol* and *acetylphlorinic nitrile*[81], $CH_3COOC_6H_4CH_2CH_2CN$.

The behavior of *cinnamonitrile* is exceptional. This nitrile reacting with phloroglucinol in the presence of hydrogen chloride yields the imide of 5,7-dihydroxy-4-phenyl-3,4-dihydrocoumarin[31],



2,4,6-Trihydroxy-5-*iso*amylacetophenone, m.p. 188°, has been prepared from *isoamylphloroglucinol* and *acetonitrile*[32]. *Iso*amylphloroglucinol has been condensed with *methyl 2-cyanomethyl-4,5-dimethoxyphenoxyacetate*, and from the keto compound obtained by the hydrolysis of the ketimine formed, *sumatrol* has been synthesized by condensation with acetic anhydride followed by hydrolysis[33].

Hydrocotoin,



(m.p. 98°)

has been prepared through the interaction of *phloroglucinol dimethyl ether* and *benzonitrile*, *iso*hydrocotoin, m.p. 177°, forming as a by-product[77].

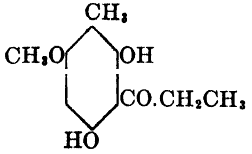
Acetyl cyanide reacting with phloroglucinol dimethyl ether gives the dimethyl ether of phloroacetophenone, together with a second compound which is probably 1-hydroxy-3,5-dimethoxy-2,6-acetylbenzene[65].

Houben and Fischer[34] prepared the following condensation products with *phloroglucinol methyl ethers* and the appropriate nitriles:

Acetophloroglucinol trimethyl ether, m.p. 100–103°
Protocotoin, $(CH_3O)_2OH.C_6H_2.CO\ C_6H_4O_2CH_2$
*iso*protocotoin
Methylprotocotoin, $(CH_3O)_3C_6H_2.CO.C_6H_3O_2CH_2$
Cotogenin, $(CH_3O)_3C_6H_2.CO.C_6H_3(OH)_2$

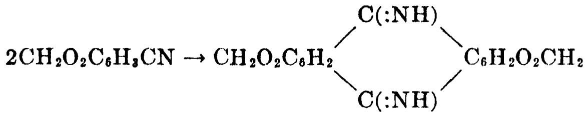
Shriner and Stephenson[35] prepared 2,6-dihydroxy-3,4-dimethoxy-α-p-methoxyphenylacetophenone, m.p. 116.5°, from 4,5-dimethoxyresorcinol and homoanisonitrile, $CNCH_2C_6H_4OCH_3(p)$.

Arfidinol,



has been prepared from ***methylphloroglucinol-β-monomethyl ether*** and ***butyronitrile***. The compound exists in two isomeric forms, one melting at 140–141°, the other at 156–160°[78]. 2,4-Dihydroxy-ω-3,6-trimethoxyacetophenone, m.p. 150–151°, has been obtained through the condensation of ***methoxyacetonitrile*** with 2,5-dimethoxyresorcinol[79].

Piperonylic nitrile condenses with itself in chloroform solution under the action of chlorosulfonic acid to 2,3,6,7-dimethylenetetraoxyanthraquinone diimide[48]:



$$2CH_2O_2C_6H_3CN \rightarrow CH_2O_2C_6H_2\begin{matrix} \diagup C(:NH) \diagdown \\ \diagdown C(:NH) \diagup \end{matrix}C_6H_2O_2CH_2$$

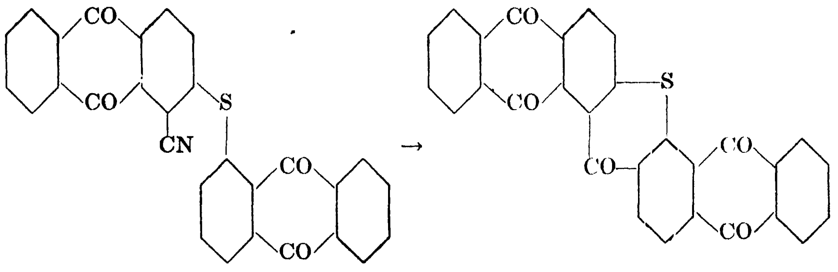
3,4-Dimethoxy- and 3-methoxy-4-ethoxybenzonitrile give similar dimers[49].

Other Condensations. *β-Naphthol* reacts with *acetonitrile* to form exclusively acetimino-β-naphthyl ether hydrochloride, $C_{10}H_7.O.C(:NH).CH.HCl$. *α-Naphthol* gives both acetimino-α-naphthyl ether hydrochloride and *p*-hydroxyacetonaphthonimide hydrochloride; the latter does not react further with acetonitrile to form an iminoether[41].

A mixture of *1:8-acenaphthene* and *cyanoacetic acid* heated to melting with sodium aluminum chloride gives a ring keto-ketimine in which the keto and ketimine groups are attached at the 4 and 5 positions[42]. Ring diketimines of similar type result from the interaction of naphthalene, acenaphthene, or anthracene with malononitrile on melting a mixture of the two compounds with sodium aluminum chloride[43].

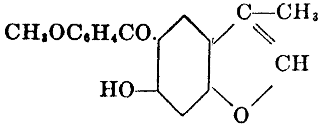
Anthranol methyl ether condensed in the presence of aluminum chloride with *acetonitrile* in ethereal solution and with *benzonitrile* in benzene solution gives 10-methoxy-9-anthryl methyl ketimine and 10-methoxy-9-anthryl phenyl ketimine. Heated with 2-normal hydrochloric acid these compounds are converted to anthron. The corresponding ethyl-, *p*-tolyl-, benzyl- and *p*-chlorophenyl ketimines have also been prepared from anthranol methyl ether and the appropriate nitriles[44].

Thioxanthones have been prepared by heating sulfides of *anthraquinone nitriles* with sulfuric acid[66]:



Karrer and co-workers[37] obtained depsenones through the condensation of 2-*methyl*-5-*hydroxycoumarone* with various nitriles.

They prepared:
2-Methyl-5-hydroxydepsenone, m.p. 158° with benzonitrile;
2-Methyl-5-hydroxy-4′-methoxydepsenone,

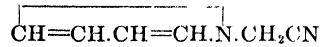


(m.p. 178°) with anisonitrile;

2-Methyl-5,4′-dihydroxydepsenone, m.p. 298° with *p*-hydroxybenzonitrile:
2-Methyl-5,3′,4′-trihydroxydepsenone, m.p. 250°, with protocatechunitrile.

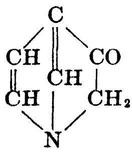
Tetrahydroeuparin has been obtained through the condensation of 6-hydroxy-2-*iso*propylcoumarin with acetonitrile and subsequent hydrolysis of the resulting ketimine[88].

N-Cyanomethylpyrrole



$$\overline{\text{CH=CH.CH=CH.N}}\text{.CH}_2\text{CN}$$

which is obtained through the interaction of potassium pyrrole and chloroacetonitrile in benzene solution, subjected to self-condensation by the Houben-Hoesch procedure[67], forms a compound melting at 307–308° which may be



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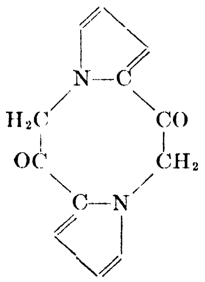


Fischer and co-workers prepared 5-keto derivatives of *2,4-dimethyl-3-carbethoxypyrrole* by reacting this compound with *acetonitrile*, *benzonitrile*, *chloroacetonitrile*, *cyanogen*, *malononitrile*, *ethyl cyanoacetate;* 5-keto derivatives of *2,5-dimethyl-3-carbethoxypyrrole* by reaction with *chloroacetonitrile*, *ethyl cyanocarbonate;* 3- and 5-keto derivatives respectively from *2,4,5-trimethylpyrrole*, *2,4-dimethyl-3-acetylpyrrole* by reacting the former with *chloroacetonitrile*, the latter with *ethyl cyanocarbonate*[46]. Keto derivatives have also been made through the interaction of *2,4-dimethylpyrrole* with *acetonitrile* and of *2,4-dimethyl-5-carbethoxypyrrole* with *chloroacetonitrile*[47].

2-Methylindole has been condensed with *acetonitrile*, *benzonitrile* and *benzyl cyanide* and from the ketimines formed 2-methyl-3-acetylindole (m.p. 195–196°), 2-methyl-3-benzoylindole (m.p. 181–182°) and 2-methyl-3-phenylethanone indole (m.p. 196–197°) have been obtained in 33, 75 and 80% yield respectively. The reaction takes place in ethereal solution without the use of a catalyst. 2-Methyl-3-aminoacrylic ethyl ester, m.p. 135° has been obtained from 2-methylindole and *ethyl cyanoacetate* in 70% yield[45].

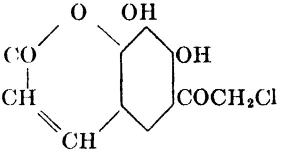
Reaction with Chloroacetonitrile and Other Chlorinated Nitriles

Chloroacetonitrile reacts with resorcinol to form the ketimine of 5-hydroxycoumaranone which, on hydrolysis, yields 5-hydroxycoumaranone[23]. Condensation between *β-chloropropionitrile* and resorcinol takes place almost exclusively in the following manner[24]:

$$C_6H_4(OH)_2 + Cl.CH_2CH_2CN \rightarrow C_6H_3(OH)_2.CH_2CH_2CCl{:}NH$$

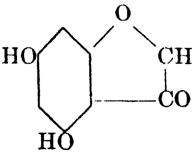
The chlorimine condenses to hydroxychromanoneimide from which, on hydrolysis, hydroxychromanone is obtained[24]. *β-Chlorobutyronitrile* reacts with resorcinol in a similar manner to form γ-2:4-dihydroxyphenylbutyronitrile which may be hydrolyzed to the corresponding acid[25]. Resorcinol condensing with *α-chloroisobutyl cyanide* in the presence of zinc chloride and hydrochloric acid gives, upon hydrolysis of the addition product first formed, 2-*iso*propyl-6-hydroxycoumaranone, $C_{11}H_{12}O_3$, needles melting at 174–175°[63].

Pyrogallol condensed with *chloroacetonitrile* in the presence of zinc chloride and hydrochloric acid forms the ketimine of ω-chlorogallacetophenone, $(HO)_3$-$C_6H_2.COCH_2Cl$, m.p. 169–170°. This compound, condensed with malic acid in the presence of sulfuric acid forms 6-chloracetyl-7,8-dihydroxycoumarin,



yellow plates, m.p. 228–229° (dec.)[64].

ω-Bromoresacetophenone dimethyl ether, m.p. 101–102°, has been obtained from *resorcinol dimethyl ether* and *bromoacetonitrile*, and ω-bromoresacetophenone, m.p. 127°, from *resorcinol* and bromoacetonitrile[70]. Chloroacetonitrile condensed with *phloroglucinol* gives 2,4,6-trihydroxyphenyl chloromethyl ketimine, which by hydrolysis and subsequent condensation in presence of sodium acetate is converted to the compound[36]



Phloroglucinol trimethyl ether condensed with chloroacetonitrile gives upon hydrolysis of the ketimine first formed, 1,3,5-trimethyoxy-ω-chloroacetophenone, m.p. 95–96° in 80% yield; the corresponding bromo compound, melting at 86° has also been made from bromoacetonitrile. Condensation with α-bromo-β-phenylpropionitrile gives the trimethyl ether of ω-bromo-ω-benzyltrimethylphloroacetophenone, m.p. 101–102° in 45% yield[80].

Abnormal Behavior of Trichloroacetonitrile. Trichloroacetonitrile condenses with aromatic compounds more readily than unchlorinated nitriles. The resulting ketimines may be readily decomposed with alkalies to chloroform and a nitrile[4]:

$$o\text{-}CH_3C_6H_4.CNH.CCl_3.HCl + NaOH \rightarrow o\text{-}CH_3C_6H_4CN + HCCl_3 + NaCl + H_2O$$

Houben and Fischer[6] report the following yields of ketimine and nitrile from various aromatic compounds:

	Yield of Ketimine, %	*Yield of Nitrile,* %
Toluene	80	75
m-Xylene	80	96
p-Xylene	66	98
Mesitylene	73	100
Tetralin	42	14
Phenol	18	25
1,4,5-Xylenol	70	100
3,5-Dimethylanisol	74	89
Thymol	50	81
Carvacrol	66	62

Nitriles were obtained also from 2-methylindole, benzene, and methylanisole in the yields 95, 69, and 67 %, respectively.

Houben-Hoesch Syntheses with Trichloroacetonitrile. While nitriles in general do not yield ketimines with benzene and its homologues, and with monohydric phenols or their ethers, trichloroacetonitrile may be readily condensed with these compounds to trichloroacetophenone derivatives. Houben and Fischer[26,39] prepared the following compounds in the yields indicated:

	Yield, %
ω-Trichloroacetophenone, $C_6H_5COCCl_3$	70
Trichloromethyl-*p*-tolyl ketone, $CH_3C_6H_4COCCl_3$	93
Trichloromethyl 3,4-dimethyl-phenyl ketone, $(CH_3)_2C_6H_3.COCl_3$	60
Trichloromethyl 2,4-dimethyl-phenyl ketone, $(CH_3)_2C_6H_3.COCl_3$	94
Trichloromethyl 1,5-dimethyl-phenyl ketone	83
Trichloroacetylnaphthol	29
p-Trichloroacetylphenol, $Cl_3CCOC_6H_4OH$	95
p-Trichloroacetyl-*o*-xylenol, $Cl_3CCO.C_6H_3(CH_3)OH$, m.p. 88–90°	40
3-Methyl-2-trichloroacetylphenol	37
3-Methyl-4-trichloroacetylphenol, m.p. 84–87°	73
2-Trichloroacetyl-5-methylphenol	37
o-Trichloroacetyl-*p*-cresol methyl ether, $Cl_3CCO.C_6H_4(CH_3O)CH_3$, m.p. 46–49°	71
4-Methyl-6-trichloroacetylphenol	11

The yields of ketone obtained by Houben and Fischer from various phenol ethers and trichloroacetonitrile are given in the following table:

Phenol Ether	*Yield of Ketone,* %
Anisol	70
Phenetol	80–83
o-Cresol ethyl ether	86
m-Cresol ethyl ether	79
p-Cresol ethyl ether	50–70
o-Bromanisol	5
Salicylic acid methyl ether	little
Diphenyl ether	10

Houben and Fischer[3] condensed α-naphthol with acetonitrile, mono- and trichloroacetonitriles, benzonitrile and benzyl cyanide, and obtained ketones in 38, 55, 50, 18 and 40% yields, respectively. α-Naphthol ethyl ether gave, with acetonitrile, chloroacetonitrile and trichloroacetonitrile ketones in 2–5, 85 and 96% yields, respectively. 5-Trichloroacetyl-2,4-dimethylpyrrole has been obtained through the interaction of dimethylpyrrole and trichloroacetonitrile in the presence of hydrogen chloride and hydrolysis of the ketimine formed[68].

Resorcinol dimethyl ether has been condensed with trichloroacetonitrile giving the ketimine of ω-trichlororesacetophenone dimethyl ether in quantitative yield[3].

Application of the Method to Cyanogen Bromide and Cyanogen

Karrer[50] applied the Houben-Hoesch synthesis to cyanogen bromide. The product of the reaction with resorcinol, after hydrolysis of the imine first formed, was 2,4-dihydroxybenzaldehyde. This led Karrer to conclude that cyanogen bromide does not show any tendency to form a chloro bromimide, BrC(:NH)Cl. This was in harmony with the conclusion previously arrived at by Nef[51] that cyanogen chloride does not form a chlorimide with hydrogen chloride.

Cyanogen reacts with benzene and its homologs in the presence of aluminum chloride to form an iminonitrile, RC(NH).CN, which on hydrolysis forms the corresponding ketonitrile. Thus, benzoyl cyanide is obtained from benzene. *p*-Methylbenzoyl cyanide is obtained from toluene and *p*-ethylbenzoyl cyanide from ethyl benzene. Simultaneously, a simple nitrile also forms as a result of the introduction of the nitrile group in the benzene nucleus. A small quantity of benzonitrile forms in the reaction with benzene. The iminonitrile may be made to condense with another molecule of hydrocarbon. Thus, from benzene the diimine of benzil, $C_6H_5C(NH).C(NH).C_6H_5$, has been obtained. Iminonitriles also form from phenol ethers[52].

Karrer and Ferla[53] condensed cyanogen with resorcinol and orcinol by the Houben-Hoesch method. With resorcinol, the reaction proceeded in two steps as follows:

$$C_6H_4(OH)_2 + (CN)_2 + HCl \rightarrow (HO)_2C_6H_3C(NH).C(NH).Cl$$
$$C_6H_4(OH)_2 + C_6H_3(OH)_2.C(NH).C(NH)Cl \rightarrow (HO)_2C_6H_3C(NH).C(NH)C_6H_3(OH)_2$$

With orcinol, the reaction only proceeded to the first stage and the final product of hydrolysis was orcylglyoxylic acid, $(HO)_2C_6H_2(CH_3)CO.COOH$.

Application of the Method to Thiocyano Compounds

Kaufmann and Adams applied the Hoesch synthesis to thiocyano compounds and found that the reaction proceeds normally, the product being an iminothiol ester; thus, with resorcinol:

$$C_6H_4(OH)_2 + RSCN + HCl(+ ZnCl_2) \rightarrow C_6H_3(OH)_2C(:NH).SR.HCl\ (+ ZnCl_2)$$

The iminothiol group enters the *para*-position with respect to one of the hydroxyl groups. The free iminothiols were readily liberated with sodium bicarbonate, and were found to be stable compounds. They were converted to thiol esters by hydrolysis.

Kaufmann and Adams[54] prepared the following compounds:

Methylthiol-beta-resorcylimide hydrochloride, $(HO)_2C_6H_3C{:}NH.SCH_3.HCl$, m.p. 244–245° (dec.)

Ethylthiol-beta-resorcylimide hydrochloride, m.p. 229.5–231.5° (dec.)

n-Butylthiol-beta-resorcylimide hydrochloride, m.p. 226–228° (dec.)

Phenylthiol-beta-resorcylimide hydrochloride, m.p. 220–222° (dec.)

Methylthiol-2,4,6-trihydroxybenzoimidehydrochloride, m.p. 255–256°.

Borsche and Niemann[55] prepared the following compounds:

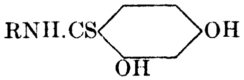
2,4-Dihydroxybenzimidothiophenyl ether hydrochloride, dec. at 222°. (The free ether melts at 150–152°).

1-Methyl-3,5-dihydroxybenzimidothiophenyl hydrochloride, m.p. 220°

2,4,6-Trihydroxybenzimidothiophenyl ether hydrochloride m.p. 232–233° (dec.)

Application of the Method to *Iso*thiocyanates

Karrer and Weiss[56] have applied the Houben-Hoesch synthesis to *iso*thiocyanates and have prepared compounds of the type



$$(OH)_2C_6H_4 + RN{:}C{:}S + HCl \rightarrow (OH)_2C_6H_3CS.NH.R$$

Mayer and Mombour[57] have prepared 2,4-dihydroxybenzene-1-thioncarboxylic anilide, m.p. 182° and 1-hydroxynaphthalene-2-thiocarboxylic anilide, m.p. 207°, by this method.

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Chapter 14

Reaction of Grignard Reagents with Nitriles

Nitriles react with Grignard compounds, normally to form imino compounds, which on hydrolysis give ketones[1,2]:

$$R.CN + R'MgI \rightarrow RR'C{:}N.MgI$$
$$RR'C{:}N.MgI + 2H_2O \rightarrow RR'CO + IMgOH + NH_3$$

Ralston and Christensen[2] prepared:

Diphenyl heptadecyl ketone from stearonitrile and diphenylmagnesium bromide

Diphenyl tridecyl ketone from palmitonitrile and diphenylmagnesium bromide

Phenoxyphenyl heptadecyl ketone from stearonitrile and phenoxyphenylmagnesium bromide

Phenoxyphenyl undecyl ketone from lauronitrile and phenoxyphenylmagnesium bromide

p-Methoxyphenoxyphenyl heptadecyl ketone from stearonitrile and *p*-methylphenoxyphenylmagnesium bromide

2-Furyl undecyl ketone from lauronitrile and 2-furylmagnesium iodide

2-Dibenzofuryl heptadecyl ketone from stearonitrile and 2-dibenzofurylmagnesium bromide

2-Dibenzofuryl undecyl ketone from lauronitrile and 2-dibenzofurylmagnesium bromide

α-Naphthyl heptadecyl ketone from stearonitrile and α-naphthylmagnesium bromide

α-Naphthyl undecyl ketone from lauronitrile and α-naphthylmagnesium bromide

The procedure was to add the nitrile drop by drop into the solution of the magnesium complex, and to heat the mixture under a reflux condenser until the reaction was complete. Gilman and Schulze's[3] color test for Grignard reagents was made use of to determine the end of the reaction.

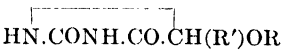
Methoxyacetonitrile reacts normally with *p*-methoxyphenylmagnesium bromide to form the ketimine magnesium bromide of ω-4-dimethoxyacetophenone, from which the latter is obtained by hydrolysis[4];

$$CH_3OCH_2CN + CH_3OC_6H_4MgBr \rightarrow CH_3OC_6H_4C(NMgBr).CH_2OCH_3$$
$$\rightarrow CH_3OC_6H_4CO.CH_2OCH_3$$

Methoxyacetonitrile reacts similarly with 6-methoxy-β-naphthylmagnesium bromide to form the ketimine magnesium bromide of 6-methoxy-β-naphthomethoxymethyl ketone[5].

Sommelet[6] prepared the following ketones from *ethoxyacetonitrile* and the appropriate organomagnesium iodide:
Ethoxyacetone, $C_2H_5OCH_2COCH_3$; α-ethoxybutanone, $C_2H_5O.CH_2CO.C_2H_5$; α-ethoxypentanone, $C_2H_5OCH_2CO.C_3H_7$; α-ethoxymethylpentanone, $C_2H_5OCH_2COCH$-

$(CH_3)_2$; ω-ethoxyacetophenone, $C_2H_5OCH_2COC_6H_5$. Other ether-ketones, $ROCH_2COR'$, have been made through the interaction of nitriles, $ROCH_2CN$, and Grignard compounds, R'MgBr, followed by hydrolysis of the ketimine first formed. These have been converted to aminonitriles, $ROCH_2C(R')(NH_2)CN$, with ammonium cyanide, and finally to ureidonitriles, $ROCH_2CR'(CN)NH.CONH_2$, by treatment with potassium cyanate; the ureidonitriles have been cyclized with hydrochloric acid to[7]



$$HN.CONH.CO.CH(R')OR$$

Ramart-Lucas and Legagneur[8] have prepared the following by reaction of the nitriles with phenylmagnesium iodide:

Trimethylacetophenone from trimethylacetonitrile, yield 72%

Methylethylphenylacetophenone, b.p.$_{16}$ 187–9° from methylethylphenylacetonitrile, yield 55%

Diethylphenylacetophenone, m.p. 48–49°, b.p.$_{35}$ 218°, from diethylphenylacetonitrile

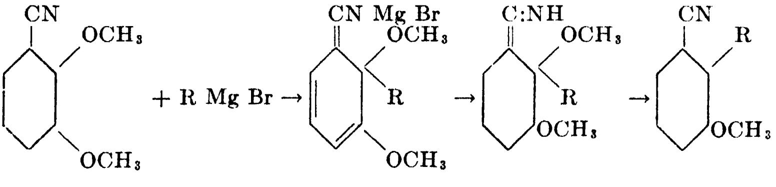
Ethylbenzylphenylacetophenone, m.p. 112–113°, from ethylbenzylphenylaetonitrile, yield 65–70%

Diphenylisopropylacetophenone, m.p. 98°, from diphenylisopropylacetonitrile, yield 90%

These workers found that benzylacetonitrile reacts very slightly with phenylmagnesium bromide. With benzylmagnesium chloride, this nitrile forms triphenylethane, $(C_6H_5)_2CH.CH_2C_6H_5$. Similarly, triphenylacetonitrile reacts with benzylmagnesium chloride to form triphenylmethane.

Benzonitrile reacting with benzylmagnesium chloride gives 50 to 55% phenylbenzyl ketimine, 10 to 15% of a dimeric ketimine, 3,4,5,6-tetraphenylhexahydro-1,2-diazine, and 5% of a product of the condensation of the ketimine and nitrile in molecular proportions, 3,4,5-triphenylpyrazoline[9].

2,3-Dimethoxybenzonitrile reacts with aliphatic Grignard compounds R Mg Br to give, after hydrolysis of the addition compound, 2-alkyl-3-methoxybenzonitrile, the reaction proceeding according to the following scheme[63]:



Compounds in which R = methyl, ethyl, *iso*propyl, *iso*butyl, cyclohexyl have been prepared. Phenyl magnesium bromide gives the 2-phenyl nitrile and phenyl 2,3-dimethoxyphenyl ketone in equal quantities. The nitriles are difficult to hydrolyze.

3,5-Dimethoxybenzonitrile reacts with *iso*butylmagnesium bromide to form 3,5-dimethoxyphenyl*iso*butylketiminemagnesium bromide, which on hydrolysis gives the corresponding ketone[10]: $(CH_3O)_2C_6H_3.CO.CH_2CH(CH_3)_2$.

3,4,5-Trimethoxybenzonitrile reacts normally at 40° with *iso*butylmagnesium bromide to form 3,4,5-trimethoxyphenyl*iso*butylketimine magnesium bromide. Reactions proceeding in other directions are favored when a four-to-one excess of the Grignard reagent is used, and the reaction mixture is subjected to prolonged heating at 110°. The products obtained under these conditions appear to be 3,5-dimethoxy-4-hydroxyphenyl *iso*butyl ketone and 3,5-dimethoxy-4-*iso*butylphenyl *iso*butyl ketone[11].

Aromatic Grignard compounds, RMgBr, reacting with *benzaldehyde cyanohydrin* give ketimines which on hydrolysis form *benzoïns*, $C_6H_5CH(OH).CO.R$. Benzoïns have thus been made from *o*- and *p*-tolyl-, anisyl-, and α-naphthylmagnesium bromides. Aliphatic and cycloaliphatic magnesium halides similarly give ketoalcohols; thus acetyl-, propionyl- and γ-cyclohexoylphenylcarbinols have been prepared from methyl-, ethyl- and cyclohexylmagnesium bromides and benzaldehyde cyanohydrin[12].

1-Cyanoanthracene is transformed by reaction with ethyl magnesium iodide to the ketimine of 1-propionylanthracene, from which the latter may be obtained by hydrolysis. 1-Benzoyl-, 1-toluoyl- and 1-naphthoyl- derivatives of anthracene have also been prepared from the appropriate organomagnesium compound and 1-cyanoanthracene. A benzoyl derivative has also been made from *2-cyanoanthracene*[13].

The reaction may proceed in an abnormal manner with the nitrile group or may assume a complex character if reactive groups other than the nitrile group are present in the molecule.

Reaction with Aminonitriles

α-Aminonitriles may react with Grignard compounds in one of three possible ways:

$$R.CH(NR'_2).CN + R''MgX \rightarrow \begin{cases} RCH(NR'_2).R'' & (1)\\ RCH(NR'_2)C(R''){:}NMgX & (2)\\ R.CH(NR'_2).CH(NR'_2).R & (3)\end{cases}$$

Reaction (2) predominates when R = H. Reaction (2) also predominates when R is a lower alkyl residue and R″ is an alkyl residue. Reaction (1) predominates if R′ is a phenyl or benzyl group. Reaction (1) also predominates when R is a phenyl group[14].

Reaction (1) is given by α-methyl-α-dimethylaminobutyronitrile, $C_2H_5C(CH_3)(CN).N(CH_3)_2$, and α-methyl-α-piperidobutyronitrile, $C_2H_5C(CH_3)(CN).NC_5H_{10}$, reacting with ethyl- and phenylmagnesium bromides and benzyl magnesium chloride; by α-dimethylaminobutenenitrile, $CH_2{=}CH.CH(CN)N(CH_3)_2$, and α-piperidobutenenitrile, $CH_2{=}CH.CH(CN)NC_5H_{10}$, and α-dimethylaminopentenenitrile, $CH_3CH{=}CH.CH(CN)N(CH_3)_2$, reacting with phenylmagnesium bromide[50]. Reaction (1) is also given by phenyl-α-piperidoacetonitrile, $C_6H_5CH(CN)NC_5H_{10}$, reacting with phenyl- or benzylmagnesium bromide[51]. Phenyl-α (phenylamino)-acetonitrile, $C_6H_5CH(CN)NHC_6H_5$, reacting with ethylmagnesium bromide forms a compound, $C_{26}H_{24}N_2$, melting at 139° and a small amount of benzylideneaniline, $C_6H_5CH{=}NC_6H_5$; the same compounds are also formed through the reaction of the aminonitrile with phenylmagnesium bromide.

Certain aliphatic α-aminonitriles form Schiff bases on reaction with Grignard compounds, by elimination of hydrogen cyanide. This reaction takes place only with nitriles containing primary or secondary amine groups[51].

In the reaction of β-dimethylaminobutyronitrile with ethylmagnesium bromide the trimer of crotonic nitrile, m.p. 173–174°, forms[52].

Reaction with Unsaturated Nitriles

Unsaturated nitriles, in which the double-bond is in a conjugated position with respect to the CN triple bond and which are substituted in the α-position, react with Grignard reagents to form β-substituted saturated nitriles:

$$C_6H_5CH{:}C(CN).C_6H_5 + RMgX \rightarrow C_6H_5CH(R).C(C_6H_5){:}C{:}NMgX \\ \rightarrow C_6H_5CH(R).CH(CN)C_6H_5$$

Nitriles with a conjugated bond having a substituent in the β-position react normally[15]:

$$C_6H_5.C(C_6H_5){:}CHCN + RMgX \rightarrow C_6H_5.C(C_6H_5){:}C(R){:}NMgX \\ \rightarrow C_6H_5C(C_6H_5){:}CHCO.R$$

In agreement with this rule, β-methoxy-β-mesitylacrylonitrile reacts with phenylmagnesium bromide to form the imino bromide, $C_9H_{11}.C(OCH_3){:}CHC(C_6H_5){:}NH.HBr$, from which the ketoether is readily obtained by hydrolysis. A diketoimine, $C_9H_{11}.CO.CH_2C(C_6H_5){:}NH$, and the corresponding diketone are also formed simultaneously. α-Methyl-β-methoxy-β-mesitylacrylonitrile gives similar results[16]. Benzyl magnesium chloride, reacting with α-phenylcinnanonitrile, $C_6H_5CH{=}C(C_6H_5)CN$, gives a 51% yield of $C_6H_5CH_2CH(C_6H_5)CH(C_6H_5)CN$, m.p. 130–132°, and 25% of the isomeric nitrile, m.p. 88–92°[60].

Reaction with Malononitrile and Substituted Malononitriles

Malononitrile reacts with Grignard reagents to form an insoluble magnesium compound from which, on hydrolysis, malononitrile is recovered unchanged. Phenylmalononitrile heated with phenylmagnesium bromide reacts to form the compound $C_6H_5C({:}NMgBr).C(C_6H_5){:}C(C_6H_5)MgBr$. *Dibenzylmalononitrile* adds one equivalent of phenylmagnesium bromide; the resulting compound decomposes into dibenzylketeneiminemagnesium bromide and benzonitrile. The latter reacts normally with a molecule of phenylmagnesium bromide to form diphenylketiminemagnesium bromide, from which benzophenone is obtained on hydrolysis:

$$CN.C(CH_2C_6H_5)_2.CN \rightarrow C_6H_5C({:}NMgBr).C(CH_2C_6H_5)_2.CN \\ \rightarrow (C_6H_5CH_2)_2C{:}C{:}NMgBr + C_6H_5CN$$

$$C_6H_5CN \rightarrow (C_6H_5)_2C{:}NMgBr \rightarrow (C_6H_5)_2CO$$

Dibenzylacetonitrile results from the hydrolysis of dibenzylketeneiminemagnesium bromide. Similar products are obtained through the interaction of *dimethylmalononitrile* and Grignard compounds[17]. Cleavage may be avoided almost entirely by adding dimethylmalononitrile to an ethereal solution of two equivalents of phenylmagnesium bromide in the usual manner, the product of hydrolysis then consisting almost wholly of the diketimine of dimethyldibenzoylmethane.

Reaction with Miscellaneous Other Nitriles

Ethyl cyanoacetate reacts with ethylmagnesium iodide to form a magnesium iodo-compound with liberation of ethane; by further reaction, a ketiminemagnesium iodide is then formed[18]:

$$CN.CH_2COOC_2H_5 + C_2H_5MgI \rightarrow CNCH(MgI).COOC_2H_5 + C_2H_6$$

$$CN.CH(MgI).COOC_2H_5 + C_2H_5MgI \rightarrow C_2H_5C(:NMgI).CH(MgI).COOC_2H_5$$

Ethyl diethylcyanoacetate, $CN.C(C_2H_5)_2.COOC_2H_5$, reacts with phenylmagnesium bromide to form $C_2H_5OCO.C(C_2H_5)_2MgBr$, which condenses with itself and after hydrolysis gives ethyl α-diethyl-γ-diethylacetyl acetate, $(C_2H_5)_2CH.CO.C(C_2H_5)_2.CO.OC_2H_5$, b.p. 138°[19].

Ethyl cyanoformate, $CNCOOC_2H_5$, reacts with ethylmagnesium bromide giving cyanomagnesium bromide and the tertiary ketoalcohol, $C_2H_5CO.C(OH)(C_2H_5)_2$, ethyl propionate forming as an intermediate. With phenylmagnesium bromide the course of the reaction is complex and benzoïn, triphenylcarbinol and triphenylvinyl alcohol are formed; with α-naphthylmagnesium bromide the compound, $C_{10}H_7.C(:NH.HBr).C(OH)(C_{10}H_7)_2$, is obtained[20].

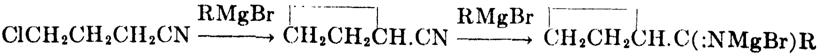
Acetonitrile reacts as a *pseudo*acid, forming a hydrocarbon[21]. With ethylmagnesium bromide it forms ethane and a compound (probably $CH_2{=}N.MgBr$) which gives acetamide when hydrolyzed[22]. Diacetonitrile[21] has also been identified in the reaction product. Hydrocarbon formation and polymerization takes place also with *propionitrile*[23], an appreciable amount of diethylketone also forming with ethylmagnesium bromide upon hydrolysis of the reaction product. *γ-Ethoxybutyronitrile*, $C_2H_5O(CH_2)_3CN$, also exhibits a *pseudo*acid character, and gives about 5% of the ketimine of ethyl γ-ethoxypropyl ketone, $C_2H_5O(CH_2)_3.CO.C_2H_5)$, with a large proportion of volatile matter, together with some dimer of the nitrile[24].

Alkyloxyacetonitriles react with allylmagnesium bromide forming products which on hydrolysis are transformed to diallylalkoxymethylcarbinamines[25], $ROCH_2C(NH_2).(CH_2.CH{:}CH_2)_2$.

Monochloroacetonitrile gives three products[26] with phenylmagnesium bromide: diphenyl, benzoylcarbinol, $C_6H_5CO.CH_2OH$, and chloroacetophenone, $C_6H_5COCH_2Cl$.

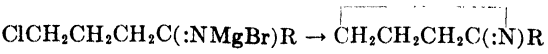
The reaction of a Grignard reagent with γ-chlorobutyronitrile, $ClCH_2CH_2CH_2CN$, proceeds in two directions:

$$ClCH_2CH_2CH_2CN + RMgBr \rightarrow ClCH_2CH_2CH_2C(:NMgBr)R$$



$$ClCH_2CH_2CH_2CN \xrightarrow{RMgBr} CH_2CH_2CH.CN \xrightarrow{RMgBr} CH_2CH_2CH.C(:NMgBr)R$$

The first reaction is of importance in that the halomagnesium derivative formed may be converted to a pyrroline, most simply by pyrolysis:



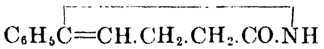
$$ClCH_2CH_2CH_2C(:NMgBr)R \rightarrow CH_2CH_2CH_2C(:N)R$$

The reaction rates of alkyl and aryl cyclopropyl ketimmonium chlorides with water at 0° increases in the order *o*-tolyl, α-naphthyl, *p*-tolyl, *m*-tolyl, phenyl and ethyl. This order is approximately the same as that in the Kharasch series[27].

Phenyl pyrrolin has been prepared in 55% yield from phenylmagnesium bromide[28] by heating an ethereal solution of the nitrile with the organomagnesium compound for two hours under reflux, distilling off the solvent, boiling in xylene until a precipitate appeared and finally hydrolyzing this. Homologs of phenylpyrrolin have also been made[28].

Phenylmagnesium bromide reacting with *δ-bromovaleronitrile* $Br(CH_2)_4CN$ gives α-phenyltetrahydropyridine[29].

Phenylmagnesium bromide reacts with *glutaronitrile* in ethereal solution forming, after hydrolysis of the initial addition product, 2-keto-6-phenyl-1,3,4-tetrahydropyridine[30],



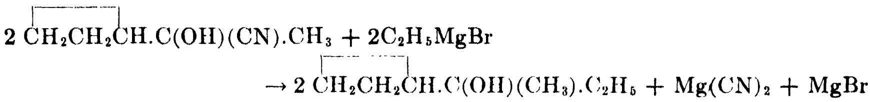
$$C_6H_5C{=}CH.CH_2.CH_2.CO.NH$$

Glutaronitrile reacting with benzylmagnesium chloride gives a base, $C_{19}H_{22}N_2$, m.p. 172°, which is probably an amidine[31].

Isodurylaldehyde cyanohydrin reacts with phenylmagnesium bromide normally to form a ketimine magnesium bromide which, however, on hydrolysis gives 2,4,6-trimethyldesylamine[32]:

$$(CH_3)_3C_6H_2.CH(OH)CN + C_6H_5MgBr \rightarrow (CH_3)_3C_6H_2CH(OH).C(:NMgBr).C_6H_5$$
$$\rightarrow (CH_3)_3C_6H_2.CO.CH(C_6H_5).NH_2$$

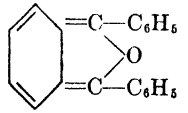
Cyclopropyl methyl ketone cyanohydrin reacts with ethylmagnesium bromide to form ethylmethylcyclopropylcarbinol[33]:



$$2\,CH_2CH_2CH.C(OH)(CN).CH_3 + 2C_2H_5MgBr$$
$$\rightarrow 2\,CH_2CH_2CH.C(OH)(CH_3).C_2H_5 + Mg(CN)_2 + MgBr_2$$

o-Cyanobenzyl bromide or *iodide* treated with methylmagnesium bromide or iodide form principally (40–43%) *sym.*-bis-*o*-cyanophenylethane, $CN.C_6H_4CH_2.CH_2C_6H_4CN$. The *para*-isomer yields amorphous products containing neither nitrogen nor halogen[34].

2-Cyanobenzaldehyde reacting with phenylmagnesium bromide forms the imine of 2-benzoylbenzhydrol, $C_6H_5C(:NH).C_6H_4.CH(OH)C_6H_5$, m.p. 120–127°; this on hydrolysis gives 2,5-diphenyl-3,4-benzofuran,

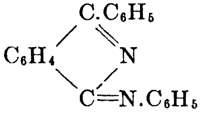


2,5-Di-*p*-methoxyphenyl-3,4-benzofuran forms similarly from *p*-anisylmagnesium iodide and 2-cyanobenzaldehyde[35].

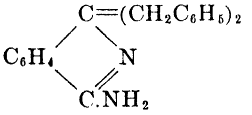
Benzyl cyanide gives with Grignard reagents in general complexes of the form[36] $C_6H_5CH(CN)MgX$; with phenylmagnesium bromide it forms the ketimine of phenyldesoxybenzoïn. *Diphenylacetonitrile* also forms a desoxybenzoïn ketimine and some tetraphenylsuccinonitrile, m.p. 204–205°[37].

Benzoyl cyanide, C_6H_5COCN, gives with phenylmagnesium bromide the compound $C_6H_5C(C_6H_5)_2OMgBr$; similarly with benzylmagnesium chloride and with ethylmagnesium bromide the compounds, $C_6H_5C(CH_2C_6H_5)_2OMgCl$, and $C_6H_5C(C_2H_5)_2OMgBr$ form. Other *α-ketonitriles* react similarly[38].

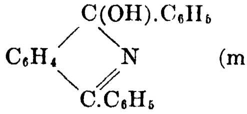
Phthalonitrile reacting with phenylmagnesium bromide in a mixture of benzene and ether gives a violet compound melting at 234–236°, which is probably phenyliminophenyl*iso*indolone[39],



With benzylmagnesium chloride a compound of the empirical formula $C_{22}H_{20}N_2$, is formed, melting at 180.5° which is probably 3,3-dibenzyl-1-amino*iso*indole[40],



Phenylmagnesium bromide gives with *ethyl o-cyanobenzoate,* 1-hydroxy-1,3-diphenyl*iso*indol,

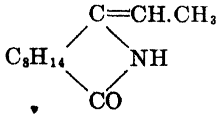


(m.p. 192.5°)

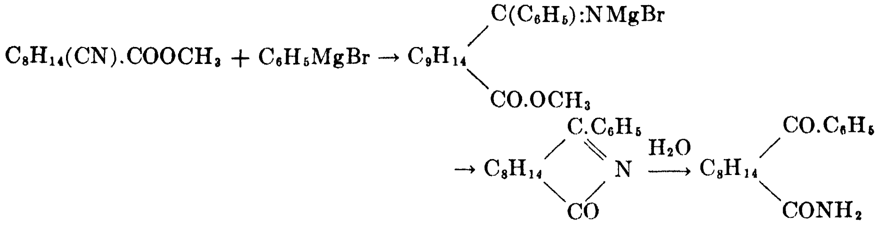
This is readily hydrolyzed to *o*-dibenzoylbenzene[41].

Acyl campholic esters may be obtained through the interaction of Grignard compounds with the *cyanocampholic methyl ester* $C_8H_{14}(CH_2CN).COOCH_3$. Other reactions may take place simultaneously; thus with phenylmagnesium halides the compounds $C_8H_{14}(CH_2CN).COC_6H_5$ and $C_8H_{14}(CH_2CO.C_6H_5).COC_6H_5$ form in addition to $C_8H_{14}(CH_2COC_6H_5)COOCH_3$ upon hydrolysis of the initial reaction product[42].

Methylmagnesium iodide reacting in ethereal solution with *α-cyanocamphoric acid esters* forms a tertiary alcohol; in toluene the magnesium compound reacts with the cyano group giving a ketoalcohol which is dehydrated to an ethylenic ketone. Ethylmagnesium bromide reacting with the methyl ester of α-cyanocamphoric acid gives α-ethylidenecamphindone,



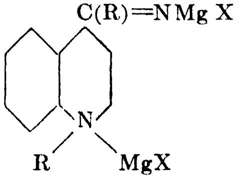
and the secondary alcohol nitrile[43], $C_8H_{14}(CN)CH(OH).C_2H_5$. Phenylmagnesium bromide gives with the methyl ester of α-cyanocamphoric acid the compounds $C_8H_{14}(COC_6H_5)_2$ and $C_8H_{14}(COC_6H_5)CONH_2$. The latter forms as follows:



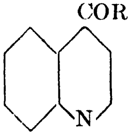
p-Tolylmagnesium bromide gives $C_8H_{14}(COC_6H_4.CH_3)_2$; ethylmagnesium bromide forms[44] α-ethylidenecamphindone, and $C_8H_{14}(CN).CHOH.C_2H_5$.

Phenylmagnesium bromide reacts with *dimethylcyanamide* to form, after hydrolysis of the intermediate magnesium compound, dimethylbenzamidine, $(CH_3)_2NC(:NH).C_6H_5$, b.p. 118°. Dimethylphenylacetamidine, $C_6H_5.CH_2.C(:NH)N(CH_3)_2$, is obtained similarly from benzylmagnesium bromide and dimethylcyanamide[45].

4-Cyanoquinoline reacts with organo magnesium compounds to form the compound



from which the keto compound



is obtained on hydrolysis[61].

Reaction with Cyanogen Halides and Cyanogen

Cyanogen chloride reacts with Grignard compounds forming iminomagnesium halides; these, on heating in water give nitriles[46]:

$$RMgX + Cl.CN \rightarrow ClC(:NMgX).R \rightarrow RCN + MgX.Cl$$

The reaction also proceeds in another direction, resulting in the formation of a chlorinated hydrocarbon:

$$RMgX + ClCN \rightarrow RCl + CNMgX$$

The nature of the hydrocarbon influences the direction of the reaction. With the aliphatic and aromatic magnesium halides the nitrile forms almost exclusively, whereas with the cycloaliphatic compounds, the chloride is the main product. This rule does not hold strictly; thus, both valeronitrile and butyl chloride are formed when butylmagnesium halides are made to react with cyanogen chloride[47], and nitriles are obtained from indene- and cyclopentadienemagnesium halides. Propiolic nitriles have been prepared by this method[59]. *Cyanogen bromide* and *cyanogen iodide* react with organomagnesium halides forming the bromine or iodine derivative of the organic radical[33].

Phenylmagnesium bromide reacting with cyanogen chloride in ethereal solution gives *sym.* phenyldichlorotriazine[62].

Dithienylketone, $C_4H_3S.CO.C_4H_3S$, has been prepared from the magnesium halo-complex, $ClC(:NMgI)C_4H_3S$, by further reaction with another molecule of magnesium compound and subsequent hydrolysis[48]:

$$ClC(:NMgX)C_4H_3S + C_4H_3SMgI \rightarrow ClMgI +$$
$$C_4H_3S.C(:NMgX)C_4H_3S \rightarrow (C_4H_3S)_2CO$$

The reaction of *cyanogen* with organomagnesium halides is similar to that of cyanogen chloride:

$$RMgX + (CN)_2 \rightarrow CN.C(:NMgX)R \rightarrow RCN + CNMgX$$
$$RMgX + (CN)_2 \rightarrow RCN + CNMgX$$

In this case, both types of reactions lead to the formation of the nitrile of the organic radical attached to magnesium[46].

Grignard and Bellet proceeded as follows: Dry cyanogen gas was conducted into anhydrous ether cooled in a freezing mixture, and the weight of dissolved cyanogen was determined by difference. The solution was placed in ice-salt mixture and the calculated quantity of the organomagnesium compound was added drop by drop and with stirring. The mixture was allowed to stand at room temperature for twelve hours, the magnesium complex was then decomposed in the usual manner and the nitrile isolated.

These reactions offered new methods for the preparation of nitriles, and Grignard and his collaborators have prepared a number of aliphatic, acetylenic, aromatic and cycloaliphatic nitriles by their use.

Reaction with *Iso*cyanides

As in the case of normal nitriles, the organic group of the Grignard compound attaches itself to the carbon atom of the *iso*cyano group on reaction with *iso*nitriles:

$$R.N:C + R'MgBr \rightarrow R.N:C(R').MgBr$$

On hydrolysis an amine and an aldehyde are formed:

$$RN:C(R')MgBr + 2H_2O \rightarrow RNH_2 + R'.CHO + MgBr(OH)$$

Reaction with Thiocyanates and *Iso*thiocyanates

Thiocyanates[49] react with alkylmagnesium halides forming a sulfide and a cyanomagnesium halide:

$$R_1SCN + R_2MgBr \rightarrow R_1SR_2 + CNMgBr$$

R_2 representing an alkyl group. With arylmagnesium halides reaction proceeds in a different manner yielding an aromatic nitrile and an organic magnesium bromosulfide:

$$R_1SCN + R_2MgBr \rightarrow R_2CN + R_1SMgBr$$

R_2 now representing an aromatic group. A mercaptan forms by the hydrolysis of the magnesium bromosulfide:

$$R_1SMgBr + H_2O \rightarrow R_1SH + HOMgBr$$

Isothiocyanates react with Grignard reagents to form substituted halogen magnesium thioamides:

$$RN{:}C{:}S + CH_3MgBr \rightarrow RN(MgBr).CS.CH_3$$

These, on hydrolysis, give substituted thioamides:

$$RN(MgBr).CS.CH_3 + H_2O \rightarrow RNH.CS.CH_3 + HOMgBr$$

Phenyl isothiocyanate reacting with excess of phenylmagnesium bromide gives *o*-phenylbenzhydrylaniline, $C_6H_5.NH.C_6H_4.CH(C_6H_5)_2$. Phenyl *iso*cyanate reacts in a similar manner forming the same compound[53].

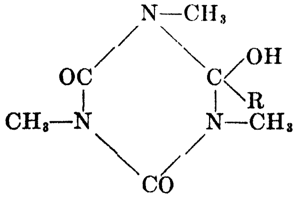
Sachs and Loevy[54] prepared thioacetanilide, thiopropionanilide, thiobenzanilide, thiobutyranilide, thio*iso*valeranilide and thio*iso*caproanilide by this reaction. Worral[55] prepared valerothioanilide, -*p*-toluide, -*p*-chloranilide, -*p*-bromanilide, -biphenylamide, -*β*-naphthylamide, and bis-thiovalero-*p*-phenylenediamide.

Isocyanates react with Grignard compounds in a similar manner forming substituted amides[56]:

$$C_6H_5N{:}CO + IMgR \rightarrow C_6H_5N{:}C(R).OMgI \rightarrow C_6H_5NH.CO.R$$

Gilman and Furry[57] prepared by this method acetic-, propionic-, *n*-butyric-, *n*-valeric-, hexahydrobenzoic-, phenylacetic-, cinnamic-, benzoic-, *p*-toluic- and *α*-naphthoic-*α*-naphthylides from *α-naphthyl isocyanate* and the appropriate organomagnesium halides.

Organomagnesium compounds, RMgX, reacting with *trimethyl isocyanurate* form, after hydrolysis of the original addition compound, 1,3,5-trimethyl-2-alcoyl (or aroyl)-2-hydroxy-4,6-dioxohexahydrotriazines



Ethyl-, *n*-propyl- and phenyl- derivatives have been prepared, melting respectively at 112–113°, 129° and 158–159°. Three atoms of bromine or iodine may be introduced directly in these compounds[58].

The reaction of nitriles with α-bromoesters and zinc resembles that with Grignard compounds, yielding a halo zinc imino-compound which is converted to a β-keto ester on hydrolysis[64]:

$$C_6H_5CN + (CH_3)_2C\,Br.COOR + Zn \rightarrow C_6H_5C(:N\,ZnBr)C(CH_3)_2.COOR \rightarrow C_6H_5.COC(CH_3)_2.COOR$$

On prolonged heating the imino compound is partially converted to an acylimino ester of the type

$$C_6H_5C[:NCOCH(CH_3)_2].C(CH_3)_2.COOR$$

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Chapter 15

Condensation Reactions Involving Active Methylenic Groups: Other Condensations

Condensation reactions may involve interactions with a reactive methylene group, the —CN group or other active groups present in a nitrile. Condensation reactions involving reactive methylene groups have provided a fertile field of research. The hydrogen atoms of a reactive methylene group, such as that in cyanoacetic ester, $CNCH_2COOC_2H_5$, are replaceable by sodium or other alkali metals. The alkali metal in these compounds may be replaced by alkyl groups by reaction with halogenated alkyls. Other halogenated compounds may also react with these sodium compounds to form condensation products.

The methylene group may also react with hydroxy compounds, carbonyl compounds and esters to form condensation products, in the two first mentioned cases by elimination of a molecule of water, in the last by elimination of a molecule of alcohol. Other types of reactions involve condensations with nitroso groups, addition to double bonds, condensation with CN— groups. These various types of reactions will be considered in the order mentioned, with the exception of the condensations with carbonyl groups, which are considered in the chapter that follows.

Alkylation of Reactive Methylenic Groups

Representative nitriles having a reactive methylene group are ethyl cyanoacetate, $CNCH_2.COOC_2H_5$, malononitrile, $CN.CH_2.CN$, and benzyl cyanide, $C_6H_5CH_2CN$. The hydrogen atoms of the methylene group in these compounds may be replaced with sodium by the action of metallic sodium on an alcoholic solution of the compounds, or by the action of sodium alcoholate or sodium amide on the nitriles dissolved in alcohol or other organic solvents. The *sodium derivative of malononitrile* may be obtained by the following method:

Two tenths of a mole of malononitrile is dissolved in 15 cc of methanol and the solution is added to a solution of sodium methylate obtained by dissolving 4.6 grams of sodium in 50 cc of methanol. The sodium salt is precipitated quantitatively by the addition of anhydrous ether and cooling. The precipitate is filtered rapidly, washed, with anhydrous ether and preserved under dry ether[1].

Sodium reacts vigorously with *ethyl cyanoacetate* in ether solution forming the sodium compound, $CNCH(Na).COOC_2H_5$, which precipitates out as a white powder[2]. Thorpe[3] believed that the compound has the structure: $CNCH:C(ONa)OC_2H_5$. Sodium ethyl cyanoacetate is decomposed on hydrolysis to sodium cyanoacetate and ethyl alcohol.

Isobutyronitrile and its analogs react with lithium dialkylamides in ether solution to form lithium nitriles:

$$(CH_3)_3CH.CN + LiN(C_2H_5)_2 \rightarrow (CH_3)_2C(Li).CN + HN(C_2H_5)_2$$

The lithium compound of *iso*butyronitrile does not condense with excess of nitrile to form the dimer of the nitrile[5]. Sodium reacts with higher primary and secondary *aliphatic nitriles*, forming the sodium compound of the amidine, $RC(NH_2){:}NNa$. With *diethylacetonitrile*, sodium diethylacetonitrile forms[6].

Kaufmann and co-workers[4] prepared the sodium compound of benzyl-cyanide by allowing the compound to react with sodium amide in ether solution.

The sodium compound of benzyl cyanide in the free state is highly unstable in air. Upon exposure, it immediately assumes a brown color, smokes, collapses and leaves a tarry residue which hardens on cooling. The compound has never been isolated in an entirely pure condition[7].

Iodine, reacting with *sodium benzyl cyanide* in alcoholic solution, gives dicyanostilbene, $C_6H_5C(CN){:}C(CN)C_6H_5$, in 70 to 90% yield. Under the same conditions the sodium compound of *methylbenzyl cyanide*, $C_6H_5CNa(CH_3)CN$, gives dimethyldiphenylsuccinonitrile[8].

Alkylation of Aliphatic Nitriles. Ziegler and Ohlinger[9] alkylated *aliphatic nitriles* by the simultaneous action of alkyl halides and sodamide upon the nitriles. When using halides having a reactive halogen, the halide and a suspension of sodamide in benzol were added gradually to a solution of the nitrile in benzol heated to about 60°. The less reactive halides were mixed with the nitrile, the mixture was heated and the suspension of sodamide in an inert liquid was added gradually.

Diethylallylacetonitrile was obtained in 90% yield by proceeding in the following manner: A third of a gram molecule of diethylacetonitrile was dissolved in 80 cc of benzol and the solution was heated to 70°; a suspension of 0.36 mole of sodamide in a mixture of 85 cc of benzol and 0.375 mole of allyl alcohol was added gradually; the liquid was then boiled until ammonia was no longer given off.

Ziegler and Ohlinger prepared alkyl- and aryl-substituted nitriles in the yields indicated.

	From	*Yield, %*
Diallylethylacetonitrile	butyronitrile	82.5
Dibenzylpropionitrile	propionitrile	quantitative
Diethylbutylacetonitrile	diethylacetonitrile	78
Di*iso*propylethylacetonitrile	α-*iso*propylbutyronitrile	45.5
Di-*n*-octylbutylacetonitrile	octylbutyronitrile	70.5
α,α-Dimethyl-γ-methoxybutyronitrile	isobutyronitrile	53.5
p-Tolyl-(mercaptoethyl)-dimethylacetonitrile	isobutyronitrile	
α,α-Diethyl-γ-diethylaminobutyronitrile	diethylacetonitrile	
n-Caproic nitrile	acetonitrile	60
Diethylacetonitrile	butyronitrile	76.5
*Iso*propylbutyronitrile	....	70.5
Mono*normal*propylpropionitrile	....	65
Monobutylbutyronitrile	butyronitrile	68

Secondary nitriles may be converted to tertiary nitriles by successive treatment with sodium and an alkyl halide. The yields are poor, ranging between 20 and 30% of theory[10].

Alkylation of Ethyl Cyanoacetate. Many alkyl-substituted derivatives of ethyl cyano acetate have been made from the sodium compound of ethyl cyanoacetate and alkyl iodides, or other alkyl halides.

Hessler[11] prepared the following substituted cyanoacetic esters by this method:

	Boiling Point °C	*Under mm*
Ethyl monomethylcyanoacetate	87–90	12
Ethyl dimethylcyanoacetate	77	9
Ethyl monoethylcyanoacetate	123–124	46
Ethyl diethylcyanoacetate	215–216	a
Ethyl monopropylcyanoacetate	215–219	a
Ethyl mono*iso*propylcyanoacetate	113	25
Ethyl di*iso*propylcyanoacetate	240	a
Ethyl mono*iso*butylcyanoacetate	223–224	a
Ethyl mono*iso*amylcyanoacetate	241	a
Ethyl di*iso*amylcyanoacetate	158–159	16
Ethyl monobenzylcyanoacetate	176–185	21
Ethyl dibenzylcyanoethylacetate, m.p. 33°	237	25

a = atm. pressure

Cope and Hancock[12] prepared the following cyanoacetic ester derivatives by the same method:

	M.p. °C	*Yield,* %
(1-Methyl-1-butenyl)-methyl	160–161	20
(1-Methyl-1-butenyl)-ethyl	162–163	20
(1-Methyl-1-butenyl)-propyl	129.5–130.5	25
(1-Methyl-1-butenyl)-*iso*propyl	120–120.5	60
(1-Methyl-1-butenyl)-methyl-N-methyl	75–76	30
(1-Methyl-1-butenyl)-ethyl-N-methyl	53–55	20
(1-Ethylpropenyl)-methyl	188.5–189.5	15
(1-Ethylpropenyl)-ethyl	174.5–175.5	30
(1-Ethylpropenyl)-propyl	152.5–153.5	
(1-Ethylpropenyl)-isopropyl	125–126	60
(1-Ethylpropenyl)-propyl-N-methyl	75–76	20
(1-Methyl-1-pentenyl)-methyl	161.5–162.5	25
(1-Methyl-1-pentenyl)-ethyl	127–128	45
(1,3-Dimethyl-1-butyl)-methyl	195–196	15
(1,3-Dimethyl-1-butyl)-ethyl	188–188.5	40
(1-Methyl-1-hexenyl)-methyl	159.5–160	50
(1-Methyl-1-hexenyl)-ethyl	113.5–114	40
(1-Propyl-1-butenyl)-ethyl	138–139	35

Propyl-, dipropyl- and allylpropylcyanoacetic esters have also been prepared[13]. Braun and Ludwig[14] have prepared the methyl-2,4-dimethylpentane-derivative, b.p. 99–105°.

Substituted ethyl cyanoacetates, $CNCH(R)COOC_2H_5$, have also been prepared by the interaction of iodides IR with the silver compound of ethyl cyanoacetate[15], $CNCHAg.COOC_2H_5$.

p-Chloronitrobenzene reacting with sodio ethyl cyanoacetate gives ethyl *p*-nitrophenylcyanoacetate, $NO_2C_6H_4CH(CN)COOC_2H_5$; this on oxidation with chromium trioxide gives ethyl-α,β-di-*p*-nitrophenyl-α,β-dicyanosuccinate, m.p. 209°. Ethyl 2,4-dinitrophenylcyanoacetate, which may be obtained by reaction of 2,4-dinitrochlorobenzene and sodio ethyl cyanoacetate, gives on oxidation 2,4-dinitrobenzoylformate, $(NO_2)_2C_6H_3CO.COOC_2H_5$, m.p. 84°. Heated with concentrated hydrochloric acid, ethyl 2,4-dinitrophenylcyanoacetate gives 2,4-dinitrophenylacetonitrile, m.p. 89°[252].

(Dialkylvinyl)-alkylcyanoacetic esters have been prepared[272]. These esters cleave under the action of alcoholic sodium ethoxide to unsaturated nitriles and diethyl oxalate according to the equation

$$R''CH{:}CR'.CH(CN)COOC_2H_5 + C_2H_5OH \rightarrow R''CH_2.CR'{:}CR.CN + CO(OC_2H_5)_2$$

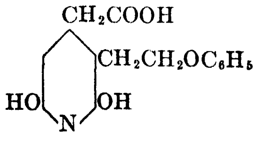
Formation of Other Substituted Ethyl Cyanoacetates. *Ethyl α-bromopropionate*, reacting with sodio ethyl cyanoacetate, forms the compound[16]: $[C_2H_5OCOCHC(CH_3)]_2C(CN)COOC_2H_5$. Ethyl α-bromobutyrate[17] and ethyl α-bromo*iso*butyrate[18], on the other hand, reacting with sodio ethyl cyanoacetate, give mono-substituted derivatives.

Ethylene dibromide reacts with sodio ethyl cyanoacetate, forming a cyclopropyl derivative[19,20]:

$$2NaCH(CN)COOC_2H_5 + BrCH_2CH_2Br$$
$$\rightarrow \overline{CH_2.CH_2.C}(CN)COOC_2H_5 + H_2C(CN)COOC_2H_5 + 2NaBr$$

A small amount of the compound, $C_2H_5OCO.CH(CN).CH_2CH_2CH(CN)COOC_2H_5$, also forms.

Ethyl α-cyano-γ-phenoxybutyrate, $C_6H_5OCH_2CH_2CH(CN)COOC_2H_5$, has been obtained by the condensation of bromo-β-phenoxyethane, $C_6H_5OCH_2CH_2Br$, with sodio ethyl cyanoacetate. The compound condenses with ethyl muconate forming an oil which is probably α-cyano-α,β-phenoxyethyl-β-carbethoxymethyladipic ethyl ester, $C_{23}H_{29}O_7N$; with ethyl β-chlorogluconate it forms the compound, $C_6H_5OC_2H_4CH(CN)C(CH_2COOC_2H_5){=}CHCOOC_2H_5$, an oil, boiling at 210° under 0.2 mm. This last, boiled with concentrated hydrochloric acid gives 2,6-dihydroxy-3-(β-phenoxyethyl)-pyridine-3-acetic acid



The hydrochloride of this melts at 146° with decomposition[222].

Ethyl α,δ-dicyanovalerate, $CN.(CH_2)_3CH(CN).COOC_2H_5$, forms upon heating ethylene dibromide with sodio ethyl cyanoacetate at 100° for five hours.

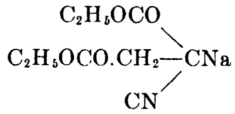
Methyl alcoholic potassium hydroxide converts the compound almost quantitatively to adipic acid[19]. Ethyl cyanocyclobutane carboxylate,

$$CH_2.CH_2CH_2C(CN)COOC_2H_5 \quad (b.p._{760} = 213\text{–}214)$$

has been obtained by condensing *α,γ-trimethylene dibromide* with sodio ethyl cyanoacetate[19]. This compound reacts with ethyl cyanoacetate, forming ethyl β-imino-α-cyanocarbethoxy-1-β-cyclobutylpropionate[21]:

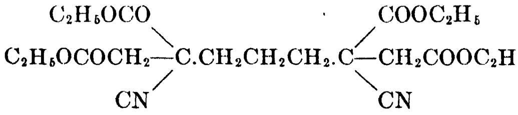
$$CH_2CH_2CH_2C(COOC_2H_5)C(:NH)CH(CN).COOC_2H_5 \quad (m.p.\ 111°)$$

α,β-Dibrompropane, reacting with sodium ethyl cyanoacetoethylacetate,



$$C_2H_5OCO.CH_2{-}C(COOC_2H_5)(CN)Na$$

gives the compound:



$$C_2H_5OCOCH_2{-}C(COOC_2H_5)(CN).CH_2CH_2CH_2.C(COOC_2H_5)(CN){-}CH_2COOC_2H_5$$

Ethyl 4-cyanotetrahydropyran-4-carboxylate has been prepared by the condensation of *β,β′-dichlorodiethyl ether* with ethyl sodiocyanoacetate[22]:

$$O(CH_2CH_2Cl)_2 + 2NaCH(CN).COOC_2H_5 \rightarrow CH_2CH_2OCH_2CH_2C(CN)COOC_2H_5 + NaCl + HCl$$

Piperidine derivatives have been prepared by the condensation of *di(β-chlorethyl)-amines* and *benzyl cyanide* in the presence of sodium amide and iodine[23]:

$$C_6H_5CH_2CN + (R_1CHCl.CH_2)_2NR_2 \rightarrow C_6H_5.C(CN).CH(R_1).CH_2.N(R_2).CH_2.CH(R_1) + 2HCl$$

Bergel and co-workers[282] prepared 4-(2-benzyloxyphenyl)-4-cyanopiperidine by condensation of 2-benzyloxyphenylacetonitrile with β,β′-dichlorodiethylamine in the presence of sodamide. 4-Substituted 4-cyanopiperidines were also made from other aromatic acetonitriles and β,β′-dichlorodiethylmethylamine.

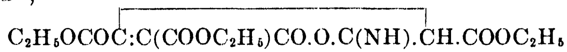
Disubstituted phenylacetonitriles, $C_6H_5C(CN)(CH_2CH_2OR)_2$, were also prepared by Bergel and co-workers[283] from benzylcyanide and halogenated ethers, $X.CH_2CH_2OR$, in which R represents the radicals $CH{:}CH_2$, CH_2OCH_3, $CH_2OC_2H_5$ and C_2H_5.

Zelinsky[24] obtained a mixture of two isomeric α,α′-dimethyl-α,α′-dicyano glutaric acids, $C_2H_5OCO.C(CH_3)(CN).CH_2.C(CH_3)(CN).COOC_2H_5$, through the interaction of *diiodomethane* and *sodium-α-cyanopropionate*, $CH_3CNa(CN).COOC_2H_5$. He also prepared trimethylcyanosuccinic ethyl ester[25] by condensing *α-bromoisobutyrate* and sodium ethyl cyanopropionate:

$$(CH_3)_2CBr.COOC_2H_5 + CH_3CNa(CN).COOC_2H_5 \rightarrow C_2H_5O.CO.C(CH_3)_2.C(CN)(CH_3).COOC_2H_5 + NaBr$$

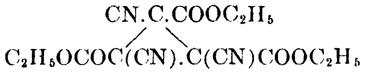
Ethyl dimethylcyanosuccinate has been prepared by the condensation of ethyl α-cyanopropionate and ethyl α-bromopropionate[26].

Sodium ethyl cyanoacetate, reacting with *ethyl bromocyanoacetate*, gives sodium ethyl dicyanoaconitate, $C_2H_5OCO.CNa(CN).C(COOC_2H_5):C(CN)COOC_2H_5$. Heated with water, this is converted to sodium ethyl dicyanoglutaconate. On boiling with dilute hydrochloric acid, ethyl dicyanoaconitate is converted to a ring compound[27],



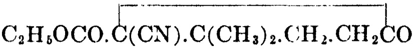
$$C_2H_5OCO\overline{C:C(COOC_2H_5)CO.O.C(NH).C}H.COOC_2H_5$$

Sodium ethyl cyanoacetate condenses in ether solution in the presence of bromine or iodine to tricyanotrimethylenetricarboxylic ester, m.p. 119.5°,



$$\begin{array}{c} CN.C.COOC_2H_5 \\ C_2H_5OCOC(CN).C(CN)COOC_2H_5 \end{array}$$

At the same time, the compound, $C_2H_5OCOCNa(CN).C(COOC_2H_5):C(CN).COOC_2H_5$, forms. These compounds form also by the reaction of sodium ethyl cyanoacetate and monobromoethyl cyanoacetate[27, 28]. The ethyl ester of γ-chloro-*iso*caproic acid, condensing with ethyl cyanoacetate, forms cyanocarboxyethyl-dimethyl-3,3-cyclopentanone[29],

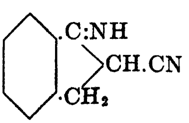


$$C_2H_5OCO.\overline{C(CN).C(CH_3)_2.CH_2.CH_2C}O$$

Ethyl chloroacetate and sodium ethyl cyanoacetate, condensed simultaneously with mandelonitrile, form β-carbethoxy-β, γ-dicyano-γ-phenylbutyric ethyl ester, $C_6H_5CH(CN).C(CN)(COOC_2H_5).CH_2.COOC_2H_5$, b.p.$_4$ 205–207°. The corresponding *p*-methoxyphenyl compound (b.p.$_3$ 232.7°) has also been prepared by the same reaction from *p*-methoxymandelonitrile[30]. From mandelonitrile, sodio ethyl cyanoacetate and β-chloroethyl propionate,the diethyl ester of α, β-dicyano-α-phenyl-*n*-butane-β,δ-dicarboxylic acid, $C_6H_5CH(CN).C(CN)(COOC_2H_5).CH_2.CH_2COOC_2H_5$, m.p. 81°, b.p.$_5$ 218–222°, has also been made by the same method[31].

p-Nitrobenzyl chloride reacts with ethyl cyanoacetate in the presence of sodium ethoxide, forming the compound $NO_2.C_6H_4CH:C(CN)COOC_2H_5$. A similar reaction takes place with *cyanoacetamide*. Malononitrile forms the compound[32], $CNCHC(NH)(OC_2H_5).CH_2C_6H_4NO_2$.

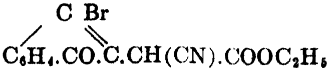
o-Cyanobenzyl chloride has been condensed with sodium ethyl cyanoacetate to α-cyano-β-*o*-cyanophenyl ethyl propionate, $CNC_6H_4CH_2CH(CN).COOC_2H_5$; from this, imino-1-cyano-2-hydrindene,



(m.p. 137°)

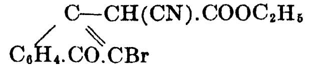
has been prepared[33].

Ethyl bromindonecyanoacetate,



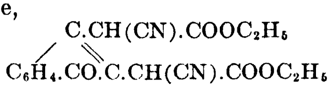
$$\begin{array}{c} C\ Br \\ C_6H_4.CO.C.CH(CN).COOC_2H_5 \end{array}$$

or



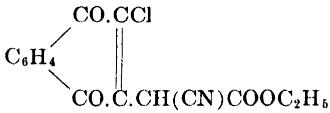
$C_6H_4.CO.CBr$ / $C—CH(CN).COOC_2H_5$

and indonedicyanoacetate,



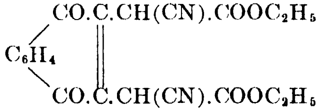
$C_6H_4.CO.C.CH(CN).COOC_2H_5$ / $C.CH(CN).COOC_2H_5$

have been obtained from *dibromindone* and ethyl cyanoacetate. Ethyl chloro-α-naphthoquinonecyanoacetate,



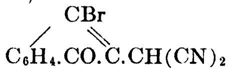
$C_6H_4(CO.CCl)(CO.C.CH(CN)COOC_2H_5)$

and ethyl α-naphthoquinonedicyanoacetate,



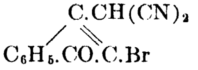
$C_6H_4(CO.C.CH(CN).COOC_2H_5)(CO.C.CH(CN).COOC_2H_5)$

have been similarly prepared from *dichloronaphthoquinone* and ethyl cyanoacetate[34]. Bromindonemalononitrile,



$C_6H_4.CO.C.CH(CN)_2$ / CBr

or

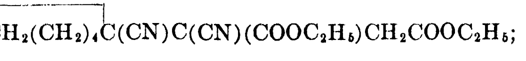


$C_6H_5.CO.C.Br$ / $C.CH(CN)_2$

has been prepared by the interaction of *dibromindone* and *malononitrile* in the presence of sodium ethoxide[35].

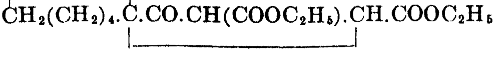
Ethyl β-cyano-α-ethyltricarballylate, $C_2H_5OCO.CH_2C(CN)(COOC_2H_5).$-$CH(C_2H_5)COOC_2H_5$, has been prepared from the sodium compound of *α-cyano-β-ethyl succinate* and *ethyl bromacetate* in 50 to 70% yield[36].

Sodio ethyl 1-cyanohexane-1-cyanoacetate has been condensed with ethyl haloacetate to diethyl 1-cyanohexane-1-cyanodiethylsuccinate



$CH_2(CH_2)_4C(CN)C(CN)(COOC_2H_5)CH_2COOC_2H_5$;

this has been hydrolyzed to 1-carboxycyclohexanesuccinic acid. The triethyl ester of this in xylene solution, heated with sodium gives cyclohexanespirocyclobutane-2-one-3,4-ethyldicarboxylate[270]



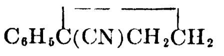
$CH_2(CH_2)_4.C.CO.CH(COOC_2H_5).CH.COOC_2H_5$

Alkylation of Benzyl Cyanide. Bodroux and Taboury[37] alkylated benzyl cyanide through the interaction of its sodium compound with alkyl iodides; the following compounds were prepared:

	Boiling Point °C	*Under mm*	*Density*	*At °C*
$CH_3CH_2CH(CN)C_6H_5$	238–240	765	0 977	14
$(CH_3)_2CH.CH(CN)C_6H_5$	245–249	765	0 967	15 5
$CH_3CH_2CH_2CH(CN)\ C_6H_5$	254–255	750	0 960	15
$(CH_3)_2CH.CH_2.CH(CN)C_6H_5$	263–266	765	0 942	16
$CH_3CH_2\ C(CN)(C_6H_5)_2$	247-249	752	0 957	16 5
$(CH_3CH_2)_2C(CN)C_6H_5$	247–249	752	0 957	16 5
$(CH_3)_2CH\ C(CN)(C_3H_7)C_6H_5$	148-150	15	0 932	16
$(CH_3)_2CHCH_2C(CN)(C_3H_7)C_6H_5$	142 5–145	15	0 940	14
$[(CH_3)_2CH\ CH_2]_2\ C(CN)C_6H_5$	152–155	15	0 931	13

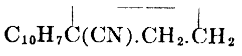
Meyer[38] found that the hydrogen atoms of the methylene group in *benzyl cyanide* are replaceable with hydrocarbon radicals; the hydrogen atom in *diphenylacetonitrile* and *methylphenylacetonitrile* is also replaceable, but that in *phenylbenzylacetonitrile*, $C_6H_5CH(CN)CH_2C_6H_5$, cannot be replaced with a hydrocarbon residue. Jullien[39] has also prepared by this reaction *alkylphenylacetonitriles* and dialkyl derivatives, such as α,α-di*iso*propyl-, α,α-di*iso*butyl-and α,α-dibenzylphenylacetonitriles. These nitriles could not be hydrolyzed with 87% sulfuric acid[40]. The dimethyl-[41], monocyclohexyl-[42] and *n*-butyl-[43] substituted derivatives have also been made. Zelinsky and Feldmann[44] prepared the methylenic compound; $C_6H_5CH(CN).CH_2.CH(CN)C_6H_5$, through the interaction of benzyl cyanide with *methylene diiodide* in the presence of sodium hydroxide. α-Phenyl-γ-hydroxybutyronitrile has been made from the sodium compound of benzyl cyanide and *ethylenechlorohydrin*[45].

Dichlorethylene condenses with monoalkylated phenylacetonitriles in the presence of sodium amide to form alkylphenyl-γ-chlorobutyronitriles in low yield[46]. *Ethylene chlorobromide* has been condensed with benzyl cyanide in the presence of sodium amide to 1-phenyl-1-cyanocyclopropane[45],



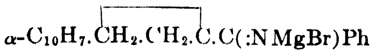
$$C_6H_5C(CN)CH_2CH_2$$

The corresponding α-naphthyl compound,



$$C_{10}H_7C(CN).CH_2.CH_2$$

m.p. 84–85°, has been obtained through the reaction of disodium α-naphthylacetonitrile with ethylene dichloride. This compound, refluxed eight hours in ethereal solution with phenylmagnesium bromide, undergoes a rearrangement, giving



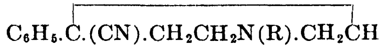
$$\alpha\text{-}C_{10}H_7.CH_2.CH_2.C.C(:NMgBr)Ph$$

from which 2-phenyl-3-(1-naphthyl)-pyrroline, m.p. 75–77° has been prepared[295].

The condensation of *dichloroisobutane* with benzyl cyanide yielding chloro*iso*butane phenylacetonitrile is followed by elimination of hydrogen chloride, and the final product of the reaction is the unsaturated compound[47], $C_6H_5CH(CN).CH{:}C(CH_3)_2$.

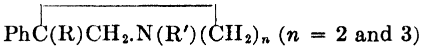
Phenylvinyloxyethylacetonitrile, $C_6H_5.CH(CN).CH_2CH_2OCH{:}CH_2$, has been prepared by the condensation of benzyl cyanide and *β-chloroethylvinyl ether* in the presence of sodium amide[48].

Bergel and co-workers[286] prepared phenyl-bis-(vinyloxyethyl)-acetonitrile and phenyl-bis-(ethyloxyethyl)-acetonitrile by a similar process and from these they finally prepared *4-phenylcyanopiperidines*,



$$C_6H_5.\overset{|}{C}.(CN).CH_2CH_2N(R).CH_2\overset{|}{C}H_2$$

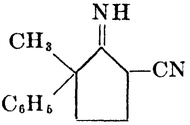
by way of phenyl-bis-(β-chloroethyl)-acetonitrile. Cyclic bases of the type



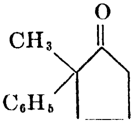
$$Ph\overset{|}{C}(R)CH_2.N(R')(\overset{|}{C}H_2)_n \quad (n = 2 \text{ and } 3)$$

were also prepared by Bergel and co-workers[287] from condensation products $C_6H_5C(R)(CN).(CH_2)_nN(R')CH_2C_6H_5$ by reduction of the cyano group to CH_2NH_2 followed by ring closure.

γ-Iodobutyronitrile reacting with phenylmethylacetonitrile in the presence of sodamide gives α-phenyl-α-methyladiponitrile $C_6H_5C(CH_3)(CN).CH_2.CH_2.CH_2.CN$; in the presence of sodamide this forms the cyclic compound



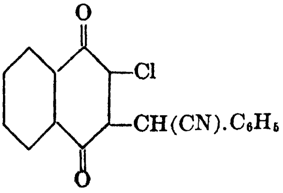
in 85% yield. Upon hydrolysis followed by decarboxylation the latter gives 2-methyl-2-phenylcyclopentanone



in 86% yield[223].

Ethyl β-cyano-β,β'-diphenylpropionate, $C_6H_5C(CN)C_6H_5).CH_2COOC_2H_5$, m.p. 103–105°, has been made by the interaction of *sodium diphenylacetonitrile* and *ethyl bromoacetate*. The compound has been hydrolyzed with boiling hydrochloric acid to α,α-diphenylsuccinic acid[49]. *Diphenyldichloroethane* has been condensed with benzyl cyanide to $(C_6H_5)_2C{:}C(CN)C_6H_5$ by heating a mixture of the two compounds at 215° for ten hours[50].

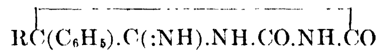
2,3-Dichloro-α-naphthoquinone reacts with sodium benzyl cyanide to form chloro-α-naphthoquinonebenzyl cyanide[51],



The compound melts at 184°. *p*-Bromomethylphenacyl cyanide, $BrC_6H_5CO.CH(CH_3)CN$, has been prepared from *p-bromophenacyl cyanide, methyl iodide* and sodium ethoxide[52].

Phenylmethylacetonitrile reacting at $-78°$ with *γ-iodobutyronitrile* in solution in a mixture of toluene and ether and in the presence of sodamide gives α-methyl-α-phenyladiponitrile in 87.5% yield. This compound, boiled for thirty minutes under reflux in benzene solution in the presence of sodamide, gives 3-methyl-3-phenyl-2-iminocyclopentyl cyanide, m.p. 96–97°, in 85% yield. 2-Phenylcylopentanone is obtained from this by hydrolysis of the nitrile group and decarboxylation, by boiling under reflux for four hours a solution of the compound in sulfuric acid containing 6% water and 6% acetic acid[281].

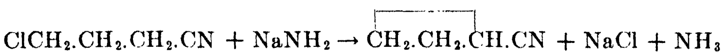
Chamberlain and co-workers[53] alkylated *phenylcarbethoxyacetonitrile* with *alkyl halides* in the presence of sodamide. The resulting nitriles were then condensed with urea in the presence of sodium ethoxide, and the imino compounds formed were hydrolyzed to 5,5-phenylalkylbartituric acids,



$$RC(C_6H_5).C(:NH).NH.CO.NH.CO$$

β-Naphthylethylphenylacetonitrile, $C_{10}H_7.CH_2CH_2CH(CN)C_6H_5$, obtained by the interaction of β-naphthylethylbromide and benzyl cyanide in the presence of sodium amide, has been converted through the Hoesch Synthesis to 1-oxo-2-phenyl-1,2-dihydrophenanthrene. Similarly, phenylethyl-β-naphthylacetonitrile, $C_6H_5CH_2CH_2CH(CN)C_{10}H_7$, obtained from phenylethyl bromide and β-naphthylacetonitrile, has been converted to α-oxo-β-(β′-naphthyl)-1,2-dihydronaphthalene[288].

γ-Chlorobutyronitrile has been converted in good yield to cyclopropane cyanide by the action of sodamide in a mixture of liquid ammonia and ether:



$$ClCH_2.CH_2.CH_2.CN + NaNH_2 \rightarrow CH_2.CH_2.CH.CN + NaCl + NH_3$$

1-Phenyl-1-cyanocyclopropane has been made in a similar manner[54].

Benzyl chloride reacting with α-sodio aliphatic nitriles forms benzyl-substituted nitriles. Butylbenzyl-, hexylbenzyl- and diethylbenzylacetonitriles have been prepared by this method[224].

Sulfonylacetonitriles, $RSO_2CH_2.CN$, reacting with *alkyl halides* and sodium ethoxide in alcohol solution yield dialkyl derivatives readily. A mono-substituted compound has been obtained only on benzylation of β-naphthylsulfonylacetonitrile[55]. β-Cyanoethyl toluenesulfonate reacts with sodioethyl malonate forming ethyl β-cyanoethylmalonate[225].

Alkylation by the Use of Alkyl Sulfates. Nitriles containing a reactive methylene group may be alkylated by means of alkyl sulfates. Thus, α-phenylpropionitrile has been made from benzyl cyanide and dimethyl sulfate; α-phenylbutyronitrile from the sodium compound of benzyl cyanide and diethyl sulfate. *Iso*propyl cyanide has been obtained from ethyl cyanoacetate by reaction with diethyl sulfate and sodium ethoxide[56].

Cyanoacetic ester has been alkylated with *diethyl sulfate* to ethyl α-cyano*iso*butyrate. *Benzyl cyanide* and *ethyl cyanoacetate* have been similarly ethylated, the yield of alkylated compound being respectively 89% and 60% of the theoretically calculated.[56]

Fuson and co-workers[57] have methylated α-cyanoacetomesitylene, $C_9H_{11}COCH_2$-CN, and α-cyanopropiomesitylene, $C_9H_{11}CO.CH(CH_3).CN$, to β-methoxy-β-mesitylacrylonitrile and α-methyl-β-methoxy-β-mesitylacrylonitrile respectively with methyl sulfate and potassium hydroxide:

$$C_9H_{11}.COCH_2.CN + (CH_3)_2SO_4 + KOH \rightarrow C_9H_{11}.C(OCH_3){=}CH.CN + KCH_3SO_4 + H_2O$$

Similarly β-methoxy-β-*p*-bromophenylacrylonitrile has been obtained from *p*-bromophenacyl cyanide by alkylation with methyl sulfate and potassium hydroxide[52].

Di- and triaryl acetonitriles have been made by the Friedel-Crafts reaction from mono- and diarylbromoacetonitriles, ArCHBr.CN, $(Ar)_2CBrCN$ and aromatic hydrocarbons. By this method were prepared α-phenyl-α-tolyl-, α-phenyl-α-(2,5-dimethylphenyl)-, α-phenyl-α-*p*-anisyl, α-phenyl-α-1-naphthyl-, di-*p*-tolyl-, α-*p*-tolyl-α-(2,5-dimethylphenyl)-, α-phenyl-α-1-naphthyl-, α-(2,5-dimethylphenyl)-α-(2-naphthyl)-, triphenyl- and α-phenyl-α,α-di-*p*-tolyl-acetonitriles[226].

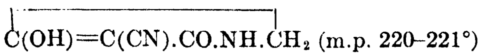
Acid chlorides reacting with aliphatic nitriles in the presence of aluminum chloride form ketonitriles[227].

Acylation of Reactive Methylenic Groups

The methylene group in cyanoacetic esters and other nitriles containing an active methylenic group may be acylated by causing the sodium compound of the nitrile to react with an acyl chloride:

$$CNCH(Na)COOC_2H_5 + ClCO.R \rightarrow CN.CH(COR)COOC_2H_5 + NaCl$$

Ethyl acetylcyanoacetate, $CH_3CO.CH(CN)COOC_2H_5$, has been prepared through the reaction of *sodium ethyl cyanoacetate* with *acetyl chloride* in alcoholic solution, at 40 to 50°. The compound may also be prepared by the action of cyanogen chloride on sodium ethyl acetoacetate[58], or by the action of potassium cyanide on chloroacetoacetic ethyl ester in alcoholic solution[59]. Chloroacetyl-, bromoacetyl- and cyanoacetylcyanoacetic esters have also been prepared. Ethyl chloroacetylcyanoacetate gives with ammonia 4-cyano-3-ketopyrrolidone[228],



$$C(OH){=}C(CN).CO.NH.CH_2 \text{ (m.p. 220–221°)}$$

Ethyl ethoxyacetylcyanoacetate, $C_2H_5OCH_2CO.CH(CN)COOC_2H_5$, has been made from *ethoxyacetyl chloride* and ethyl cyanoacetate[60]. Cyanoacetic esters have been condensed with the *chloride of monoethyloxalic acid*, C_2H_5OCO.-COCl, in the presence of sodium ethoxide to esters of ethyl cyanooxalacetate[61], $ROCOCH(CN).COCOOC_2H_5$. Benzoylcyanoacetic ethyl ester, C_6H_5COCH-$(CN)COOC_2H_5$, which can be prepared by the same method, decomposes to cyanoacetophenone on boiling with water[62]. Ethyl *o*-cyanobenzoylcyanoacetate, $CNC_6H_4COCH(CN)COOC_6H_5$, has been made from *o-cyanobenzoyl chloride* and sodium ethyl cyanoacetate[63]. The *phthalyl* compounds, $C_8H_4O_2{:}NC(R_1)(R_2)$.-

COCl, reacting with sodium ethyl cyanoacetate, form[64] $C_8H_4O_2{:}NC(R_1)(R_2).$-$CO.CH(CN)COOC_2H_5$. *p*-Phthalodicyanoacetic acid ethyl ester, $C_6H_4(CO.$-$CH(CN).COOC_2H_5)_2$, m.p. 179°, has been prepared from the chloride of *p*-phthalic acid and sodium ethyl cyanacetate by reaction in ether solution at room temperature, the reaction requiring 24 hours and the yield being 30% of the theoretical[65].

Acylcyanoacetic esters, $R_1CO.CH(CN)COOR_2$, may also be prepared through the interaction of an acyl chloride with the silver compound of a cyanoacetatic ester[66], $AgCH(CN)COOR_2$.

Methyl acylcyanoacetates condense with cyanoacetic methyl ester on warming on a water bath as follows[67]:

$$RCO.CH(CN)COOCH_3 + H_2C(CN)COOCH_3 \rightarrow CH_3OCO.CH(CN).C(OH)(R).CH(CN).COOCH_3$$

The sodium compound of *benzyl cyanide*, $NaCH(CN)C_6H_5$, reacting with an *acyl chloride*, gives an acylated benzyl cyanide. Sodiobenzyl cyanide reacts vigorously with *acetyl chloride*, and a small quantity of a resinous mass separates out. A complex series of reactions takes place[68], among others,

$$CH_3COCl + 2NaCH(CN)C_6H_5 \rightarrow CH_3C(ONa){:}C(CN)C_6H_5 + C_6H_5CH_2CN + NaCl$$

$$CH_3COCl + CH_3C(ONa){:}C(CN)C_6H_5 \rightarrow CH_3C(OCOCH_3){:}C(CN)C_6H_5 + NaCl$$

Acetic anhydride reacts similarly. With *benzoyl chloride* good yields of the benzoylated compound, $C_6H_5CO.CH(CN)C_6H_5$, are obtained. *o-Phthalic anhydride* does not react with the sodium compound of benzyl cyanide[68].

Sodium ethyl cyanoacetate reacts with *picryl chloride* to form ethyl 2,4,6-trinitrophenylcyanoacetate, m.p. 66°. *2,4-Dinitrochlorobenzene* reacts similarly to form ethyl 2,4-dinitrophenylcyanoacetate, m.p. 66°[69].

Cyanogen chloride reacts with *monosodium malononitrile* to form cyanoform:

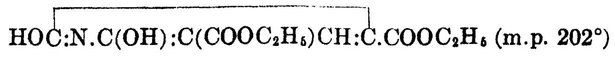
$$(CN)_2CHNa + ClCN \rightarrow (CN)_3CH + NaCl$$

Cyanogen bromide reacts in a similar manner. The latter reacts with disodium malononitrile to form the sodium compound of cyanoform, $(CN)_3CNa$. Tricyanomethyl bromoide, a *pseudo*halogen, has been prepared from the silver salt of this compound[70].

Disodium cyanoacetic ester reacts with *chloroform* to form the sodium compound of dicyanoglutaconic ester[71]:

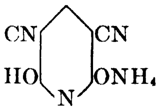
$$2\ C_2H_5OCO.C(CN)Na_2 + HCCl_3 \rightarrow C_2H_5OCO.C(CN)(Na).CH{:}C(CN).COOC_2H_5 + 3NaCl$$

The same compound is obtained also from disodium cyanoacetic ester and *carbon tetrachloride*[72]. Heated to boiling with hydrochloric acid, this compound gives ethyl dihydroxydinicotinate,



$$HOC{:}N.C(OH){:}C(COOC_2H_5)CH{:}C.COOC_2H_5 \text{ (m.p. 202°)}$$

Cyanoacetamide reacts with *chloroform* in the presence of sodium ethoxide giving the sodium compound of *α,γ*-dicyanoglutaconamide, $H_2NCO.CNa(CN)$-$CH{=}C(CN)CONH_2$, from which *α,γ*-dicyanoglutaconamide is obtained by treatment with hydrochloric acid. This compound may be partially saponified with sulfuric acid to[73] $H_2NCOCH(CN).CH{:}C(CONH_2)_2$. The compounds,



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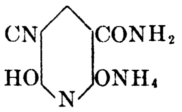


have also been made from the condensation product[74]. *Malononitrile* reacts with *chloroform* in the presence of sodium ethoxide forming the compound, $C_2H_5OC(:NH).C(CN){:}CH.CH(CN)_2$, light yellow crystals, melting with decomposition at 244°[75].

Sodium ethyl cyanoacetate reacts with *carbon tetrachloride* to form the ethyl ester of α,γ-dicyanoglutaconic acid, $C_2H_5OCO.CH(CN).CH{:}C(CN).COOC_2H_5$, m.p. 183–184°; some of the diethyl ester of α-cyano-β-iminoglutaric acid, $C_2H_5OCO.CH_2.C(NH)CH(CN)COOC_2H_5$, also forms. Sodium ethyl cyanoacetate condenses with *carbon tetrabromide* to ethyl α,α-dicyanosuccinate[76].

Dibenzoylacetonitrile, $(C_6H_5CO)_2CHCN$, is obtained by the action of sodium at ordinary temperature on a solution of *benzoyl chloride* and *acetonitrile* in ether. The compound crystallizes from boiling alcohol in fine needles, melting at 156.5°. It is not decomposed by boiling caustic solution[77].

Propionyl chloride reacts with *ethyl cyanide* in the presence of aluminum chloride to form a ketonitrile:

$$CH_3CH_2CN + ClCOCH_2CH_3 \rightarrow CH_3CH(CN).COCH_2CH_3 + HCl$$

This reaction also takes place with other nitriles and acid chlorides[78].

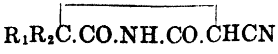
When the sodium compounds of cyanoacetoacetic acid are made to react with alkyl or acyl halides the C-derivatives of the enol form of cyanoacetoacetic acid result, such as $CH_3C(OCH_3){=}C(CN).COOCH_3$, m.p. 97°. The acetyl derivative, $CH_3C(OCOCH_3){=}C(CN)COOCH_3$, reacting with ammonia gives $CH_3C(NH_2){=}C(CN)COOCH_3$, m.p. 181°[79].

Condensation of Hydroxy Compounds with Reactive Methylenic Groups

Sodiocyanoacetic ester condenses with *aldehyde* or *ketone cyanohydrins* to form nitriles of substituted succinic acids:

$$R_1R_2.C(CN)OH + HCNa(CN).COOC_2H_5 \rightarrow R_1R_2C(CN).CNa(CN).COOC_2H_5 + H_2O$$

These nitriles may be hydrolyzed to the dicarboxylic acids[80], $R_1R_2C(COOH).CH_2.COOH$. Compounds of the type $R_1R_2C(CN).CH(CN)COOH$ have been cyclized under the action of an inorganic acid to

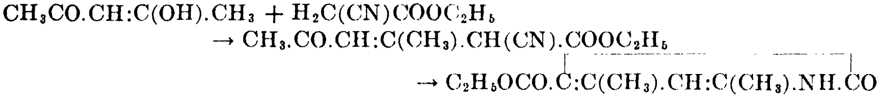


$$R_1R_2\overline{C.CO.NH.CO.C}HCN$$

The cyclic compound forms in quantitative yield if R_1R_2C is a cycloheptane ring; to the extent of 30% if R_1 and R_2 are methyl groups, and does not form at all if R_1R_2C is a cyclohexane ring[229].

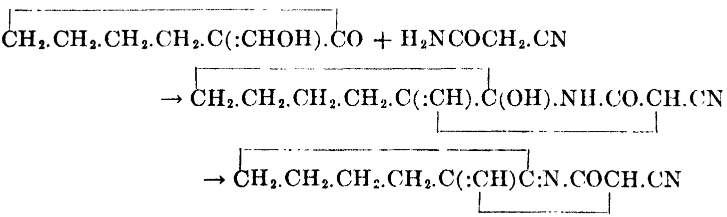
p-Methoxymandelonitrile condenses similarly with sodioethyl cyanoacetate to form the compound[30], $CH_3OC_6H_4.CH(CN).CH(CN).COOC_2H_5$, b.p.$_5$ 225°, m.p. 81°.

Ethyl cyanoacetate reacts with *acetyl acetone* to form ethyl α-cyano-δ-keto-β-methyl-Δ^{β}-hexenoate, and this condenses to ethyl 4,6-dimethyl-2-pyridone-3-carboxylate[81]:



$$CH_3CO.CH{:}C(OH).CH_3 + H_2C(CN)COOC_2H_5 \rightarrow CH_3.CO.CH{:}C(CH_3).CH(CN).COOC_2H_5 \rightarrow C_2H_5OCO.C{:}C(CH_3).CH{:}C(CH_3).NH.CO$$

Cyanoacetamide has been condensed with *hydroxymethylenecyclohexyl ketone* to a bi-cyclic compound transformation presumably taking place in the steps shown[82]:



$$CH_2.CH_2.CH_2.CH_2.C({:}CHOH).CO + H_2NCOCH_2.CN \rightarrow CH_2.CH_2.CH_2.CH_2.C({:}CH).C(OH).NH.CO.CH.CN \rightarrow CH_2.CH_2.CH_2.CH_2.C({:}CH)C{:}N.COCH.CN$$

Mandelonitrile condenses with *benzyl cyanide* in the presence of potassium cyanide to *sym.*-diphenylsuccinonitrile, $C_6H_5CH(CN).CH(CN).C_6H_5$.

N-Hydroxymethylbenzamide, $C_6H_5CONHCH_2OH$, has been condensed with diethyl α-cyanopimelate, $CNCH(COOEt)(CH_2)_4COOEt$, in presence sulfuric acid, to diethyl α-benzoylaminomethyl-α-carbamylpimelate, C_6H_5-$CONHCH_2C(CONH_2)(COOEt)(CH_2)_4COOEt$, in 91% yield[296].

Condensation of Esters with Reactive Methylenic Groups

Diethyl carbonate condenses with *aliphatic nitriles* in the presence of sodium ethoxide, forming α-carbethoxy nitriles:

$$RCH_2CN + (C_2H_5O)_2CO + (NaOC_2H_5) \rightarrow RCH(CN).COOC_2H_5 + HOC_2H_5 + (NaOC_2H_5)$$

Starting with equimolecular quantities of nitrile and sodium ethoxide, and using a three- to sevenfold excess of diethyl carbonate, Wallingford and coworkers obtained the following yields of carbethoxy nitriles from various nitriles:

Nitrile	*Yield of Carbethoxy Nitrile % of Theoretical*
CH_3CN	10
$C_3H_7.CN$	40
$(CH_3)_2CH.CH_2.CN$	47
$C_6H_{11}CN$	54
$C_{17}H_{35}.CN$	75

Vinylacetonitrile is highly reactive and gives only tarry products. Magnesium and aluminum alcoholates do not promote this reaction[83].

Nitriles, RCH_2CN, reacting with ethyl oxalate in the presence of sodium ethoxide, form cyano-α-keto ethyl esters, $CNCH(R).COCOOC_2H_5$, which are, in general, unstable. The hydroxylamine and phenylhydrazine derivatives of these compounds may be obtained in crystalline form[84]. Better yields of the keto-esters are obtained when a mixture of sodium and potassium ethoxides or potassium ethoxide alone is used instead of sodium ethoxide[84].

Acetonitrile, reacting with ethyl oxalate in the presence of sodium ethoxide, forms the sodium compound of cyanopyruvic ethyl ester, $CNCH{:}C(ONa).COOC_2H_5$. Propionitrile and other higher aliphatic nitriles react poorly or not at all[85]. Crotonic nitrile and sorbonitrile react readily with diethyl oxalate in the presence of potassium ethoxide giving $CNCH{:}CH.CH{:}C(OK)COOC_2H_5$ and $CNCH{:}CH.CH{:}CH.CH{:}C(OK)COOC_2H_5$ in 90% yield. These compounds have not been isolated in the pure form[230].

Succinonitrile, $CNCH_2.CH_2CN$, has been condensed with one and two molecules of ethyl oxalate to mono- and dioxal esters of succinonitrile, $CN.CH_2.CH(CN).COCOOC_2H_5$ and $C_2H_5OCO.CO.CH(CN).CH(CN).COCOOC_2H_5$. The latter exists in the keto and enol forms. The monooxal esters exist in two modifications[86].

Aliphatic nitriles cannot be condensed with *succinic esters*.

Acetonitrile has been converted to butyroylacetonitrile in 52% yield by reaction with sodiotriphenylmethane and *ethyl butyrate*[87].

Certain aliphatic nitriles condense with *benzoic esters* forming benzoylated nitriles in low yield[88].

Diformyl acetonitrile in the form of the sodium compound $(OCH)_2C(Na)CN$, has been prepared through the interaction of β-cyanoethylacetal $CNCH_2CH(OEt)_2$ and ethyl formate in the presence of sodium. The reaction product of this compound with aromatic amines, condensed in the presence of a dehydrating agent, gives β-cyanoquinoline derivatives[297].

Cyanoacetic esters condense with *ethyl orthoformate* giving *ethoxymethylenecyanoacetic* esters[89]:

$$CNCH_2COOR + HC(OC_2H_5)_3 \rightarrow CN.C(:CH.OC_2H_5).COOR + 2C_2H_5OH$$

Ethyl ethoxymethylenecyanoacetate, $C_2H_5O.CH{=}C(CN)COOC_2H_5$ reacting with *pseudo*ethylthiourea, $H_2NC(SC_2H_5){=}NH$, gives α-cyano-β-*pseudo*ethylthioureido ethyl acrylate, $H_2NC(SC_2H_5){:}N.CH{:}C(CN)COC_2H_5$, yellow needles, melting at 130°, and 2-ethylthio-5-carbethoxy-6-aminopyrimidine, m.p. 102–103°. The compound may also be condensed with two molecules of *pseudo*ethylthiourea forming α-cyano-β-*pseudo*ethylthioureidoacrylo*pseudo*ethylthiourea, $H_2NC(SC_2H_5){=}NH.CH{=}C(CN).CO.N{=}C(SC_2H_5)NH_2$, m.p. 164–165[231]. Ethoxymethylenemalononitrile, $(CN)_2C{:}CHOC_2H_5$, m.p. 67°, is obtained on heating for seven hours a mixture of *malononitrile* and *ethyl orthoformate* in the presence of acetic anhydride, the latter serving to eliminate the ethyl alcohol formed in the reaction. This and other similar ethoxymethylene nitriles react with sodio diethyl malonate, ethyl cyanoacetate, and malononitrile forming compounds of the type[232] $CNC(COOR){=}CH.CH(COOC_2H_5)_2$. They react with amines, $R'NH_2$, forming aminomethylene compounds of the type $CNC(:CHNHR').COOR$ or $(CN)_2C:CHNHR'$, which are converted by boiling water to hydroxymethylene compounds[90], $CNC(:CHOH).COOR$, $(CN)_2C:CHOH$. *Ethyl cyanoacetate*, reacting with *amyl formate* in the presence of a metallic cyanide, gives amyl sodioöxymethylenecyanoacetate[91], $CN.C(:CHONa).COOC_5H_{11}$.

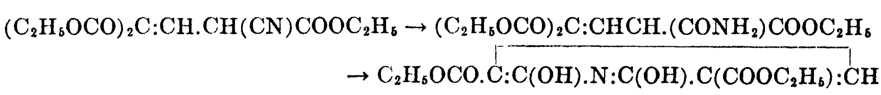
Hydroxymethylene ethyl cyanoacetate has been condensed with ethyl cyanoacetate in the presence of acetic anhydride to ethyl dicyanoglutaconate; this compound forms also through the interaction of chloromethylene ethyl cyanoacetate and ethyl chlorocyanoacetate in the presence of metallic copper[233].

Orthoacetates reacting in the presence of acetic anhydride with ethyl cyanoacetate give ethyl α-cyano-β-ethoxycrotonate, m.p. 74–75°; orthobenzoates yield ethyl α-cyano-β-ethoxy-β-phenylacrylate, m.p. 90–93°. Similar compounds are obtained through the interaction of orthoacetates and orthobenzoates with malononitrile[298].

Ethyl crotonate condensing with ethyl α-cyanopropionate forms γ-cyano-α,β-dimethylglutaric ester in 50% yield; with ethyl α-cyanobutyrate it forms ethyl γ-cyano-α-ethyl-β-methylglutarate in 30% yield. Ethyl α-ethylcrotonate reacting with ethyl cyanoacetate forms ethyl α-ethyl-β-methyl-γ-cyanoglutarate. Ethyl styrylacetate gives with ethyl cyanoacetate an ester boiling at 193°, which on hydrolysis forms β-benzyl-γ-carboxyglutaric acid, m.p. 158°. Ethyl γ-methyl-γ-phenylbutenoate reacting with sodio ethyl cyanoacetate forms ethyl γ-methyl-γ-phenyl-α-cyano-β-acetobutyrate, b.p.$_3$ = 198°[234].

Cyanoacetic ethyl ester reacts with diethyl oxalate in alcoholic solution in the presence of sodium ethoxide to form ethyl cyanoöxalacetate[92], $C_2H_5OCO.CH(CN).COCOOC_2H_5$, m.p. 98°.

Ethoxymethylmalonic diethyl ester reacting with the sodium compound of ethyl cyanoacetate forms, after the decomposition of the sodio derivative first obtained with acid, $(C_2H_5OCO)_2C:CH.CH(CN).COOC_2H_5$, and this heated with aqueous caustic solution, is converted to dihydroxydinicotinic acid ester[93]:



$$(C_2H_5OCO)_2C:CH.CH(CN)COOC_2H_5 \rightarrow (C_2H_5OCO)_2C:CHCH.(CONH_2)COOC_2H_5$$
$$\rightarrow C_2H_5OCO.C:C(OH).N:C(OH).C(COOC_2H_5):CH$$

Diethyl carbonate reacts with *benzyl cyanide* in the presence of sodamide in ether solution to form phenylcarbethoxyacetonitrile[53,94], $C_6H_5CH(CN).COOC_2H_5$.

Wallingford and co-workers carried out the reaction in alcoholic solution in the presence of sodium ethoxide using a large excess of diethylcarbonate and obtained a 78% yield of the carbethoxy nitrile. Carbethoxy compounds were also made by these authors from *p*-iodophenylacetonitrile and *p*-methylphenylacetonitrile in 50% and 87% yields, respectively. *p*-Nitrophenylacetonitrile gave tarry products and ethylphenylacetonitrile failed to react[83].

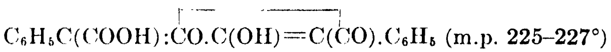
Formic esters react with benzyl cyanide to form oxymethylenebenzyl cyanide, $C_6H_5C(CN):CHOH$, m.p. 157–158°.

The triacetate of hydroxyhydroquinone reacts with hydroxymethylenebenzyl cyanide in the presence of zinc chloride forming 6,7-dihydroxy-3-phenylcoumarin, m.p. 242°[235]. *Acetic esters* reacting with benzyl cyanide give acetobenzyl cyanide[95,96], $C_6H_5.CH(CN).CO.CH_3$, m.p. 89–90°. Other aliphatic and aryl-aliphatic esters give similar compounds[95]. Thus

Propionic ester gives cyanobenzyl ethyl ketone, m.p. 58°.
Butyric ester gives cyanobenzyl propyl ketone, m.p. 107–108°.
Phenylacetic ester gives cyanodibenzyl ketone, m.p. 85–86°.
Cinnamic ester gives cinnamylbenzyl cyanide, m.p. 162–163°.

Benzyl cyanide condenses with *ethyl oxalate* in ether solution in the presence of metallic sodium to cyanophenylpyruvic ester[97], $C_6H_5CH(CN).COCOOC_2H_5$, which reacts rapidly with phenylhydrazine in hot acetic acid solution forming the corresponding phenylhydrazone, $C_6H_5CH(CN)C(:NNHC_6H_5).COOC_2H_5$, m.p. 107–108°, an isomer melting at 112–113° forming simultaneously. Hydroxylamine reacts similarly with the ester giving the oxime[98], $C_6H_5CH(CN)C(:NOH)$-$COOC_2H_5$.

Benzyl cyanide has also been condensed with diethyl oxalate to pulvinic acid dinitrile, $C_6H_5CH(CN)CO.CO.CH(CN)C_6H_5$, m.p. 132°, which is hydrolyzed to pulvinic acid[101],



$$C_6H_5C(COOH):CO.C(OH)=C(CO).C_6H_5 \text{ (m.p. 225–227°)}$$

Benzyl cyanide and *p*-methoxybenzyl cyanide condensed simultaneously with diethyloxalate in the presence of sodium ethoxide give *p*-methoxypulvinic dinitrile[236], $CH_3OC_6H_4CH(CN).CO.CO.CH(CN).C_6H_5$, dec. at 255°. Methylphenyl, chlorophenyl and β-naphthyl analogs have also been prepared by the same reaction[237].

Ethyl phenoxyacetate condensed with benzyl cyanide in the presence of sodium ethoxide gives, after decomposition of the initial product with acid, α-phenyl-α-cyano-γ-phenoxyacetone, $C_6H_5OCH_2CO.CH(CN)C_6H_5$, plates melting at 125–126°. The same type of condensation takes place with *p*-chlorobenzyl cyanide, the resulting product being α-chlorophenyl-α-cyano-γ-phenoxyacetone[99], C_6H_5-$OCH_2COCH(CN)C_6H_4Cl$, plates melting at 168°. Other aryloxyacetic esters also may be condensed with benzyl cyanide or nuclearly substituted phenylacetonitriles. Thus, *p*-nitrophenyl-2-benzyloxy-4-cyanoacetone has been obtained though in poor yield, from methyl *p*-nitrophenoxyacetate and benzyl cyanide; veratryl-2- and piperonyl-2-benzyloxy-4-cyanoacetone have been made from veratryl- and piperonylacetonitrile and the methyl ester of benzyloxyacetic acid[100].

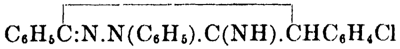
Succinic esters condense with benzyl cyanide to give diphenyldicyanoacetonylacetone[85,102], $C_6H_5.CH(CN).CO.CH_2.CH_2.CO.CH(CN).C_6H_5$.

Benzyl cyanide has been condensed with *ethyl benzoate* to cyanodesoxybenzöin[103], $C_6H_5CO.CH(CN).C_6H_5$, m.p. 91–92°, in 80% yield. Condensation products of benzyl cyanide with a few other esters, with their melting points and yields obtained, are given below:

Condensation Product	*M.P. °C*	*From*	*Yield, %*
Benzoylbenzoylphenylacetonitrile......	188	Ethyl benzoylbenzoate	97–98
*Iso*butyroylphenylacetonitrile..........	154–156	Ethyl *iso*butyrate	70
Diphenylacetylphenylacetonitrile......	97	Ethyl diphenylacetate	

With the exception of benzoylbenzoylphenylacetonitrile, which resisted hydrolysis under the most drastic conditions, these nitriles were hydrolyzed readily[104,111].

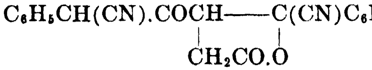
p-Chlorbenzyl cyanide has been condensed with *ethyl benzoate* to chloro-α-cyanodesoxybenzoin, $C_6H_5.CO.CH(CN)C_6H_4Cl$, m.p. 92°. This compound heated with phenylhydrazine forms 1,3-diphenyl-4-*p*-chlorophenyl-5-iminopyrazolone[105]:



$$C_6H_5C{:}N.N(C_6H_5).C(NH).CHC_6H_4Cl$$

o-Chloro-, m-bromo-, o- and p-nitrobenzoic esters do not react with benzyl cyanide; *toluyl-* and *oxalkylbenzoic esters* react to form the corresponding benzoylated benzyl acetonitriles[106]. *p*-Chlorobenzyl cyanide reacts in the same manner as benzyl cyanide[105].

Fumaric acid condenses with benzyl cyanide forming a compound of the probable structure[107]:



$$\begin{array}{l} C_6H_5CH(CN).COCH\text{——}C(CN)C_6H_5 \\ \qquad\qquad\qquad\quad CH_2CO.O \end{array}$$

2,4-Dimethoxybenzyl cyanide has been condensed with ethyl γ-(3,4-dimethoxyphenyl)-propionate in the presence of sodium ethoxide to 1-cyano-1,4-bis (3′,4′-dimethoxyphenyl)-2-butanone[299]. *o-Xylylene dicyanide* condenses with *diethyl oxalate* in the presence of sodium ethoxide to form 2,3-dihydroxynaphthalene-1,4-dinitrile in almost quantitative yield[109].

p-Xylylene cyanide, $CNCH_2C_6H_4CH_2CN$, reacts with *ethyl oxalate* in the presence of sodium ethoxide forming ethyl *p*-cyanomethylphenylcyanopyruvate[109], $CNCH_2C_6H_4CH(CN).COCOOC_2H_5$.

α-Naphthylacetonitrile condenses with *ethyl formate* in the presence of potassium ethoxide* to the potassium derivative $C_{10}H_7.C(CN){=}CHOK$, from which formyl-(naphthyl-1)-acetonitrile is obtained by hydrolysis[110].

With aniline the compound gives an anilide; reacting with phenyl isocyanate at 135°, it forms a carbanilic ester[111], $C_{10}H_7.C(CN){:}CHO.CO.NH.C_6H_5$. Formyl-α-naphthylacetonitrile cannot be directly esterified.

β-Naphthylacetonitrile also condenses with ethyl formate to give formyl-(naphthyl-2)-acetonitrile.

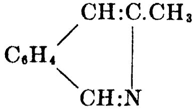
This compound reacts with iodine to form first iodoformyl-(-2-naphthyl)-acetonitrile and finally di-(-2-naphthyl)-succinonitrile, $C_{10}H_7.CH(CN).CH(CN).C_{10}H_7$.

* The reaction proceeds better when potassium alcoholate is used rather than sodium ethoxide.

Under the action of iodine in aqueous-methyl alcoholic solution in the presence of alkali, the compound forms *sym.*-di-(naphthyl-2)-dicyanoethylene[112], $C_{10}H_7.C(CN):C(CN).C_{10}H_7$.

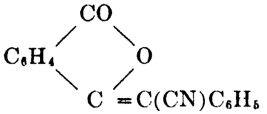
Condensations with Organic Acid Anhydrides and Salts of Organic Acids

Gabriel and Neumann condensed *o-cyanobenzyl cyanide* with the anhydrides as well as the alkaline salts of *fatty acids*. With anhydrides, they obtained products of the type $C_6H_4(CN).C(CN):C(R).OCOR$. From the condensation product with acetic anhydride they prepared 3-methyl*iso*quinoline,



The compound was also condensed with benzoyl chloride[113]. By the same reaction 3-ethyl*iso*quinoline and 3-propyl*iso*quinoline have also been prepared. Other 3-substituted *iso*quinolines may be prepared by using other acid anhydrides. When propionic anhydride is used, in addition to the normal reaction product, a compound melting at 260–261° forms which is probably[114] $CNCH_2C_6H_4C(NH).CH(CN)C_6H_4CN$.

Phthalic anhydride reacts with benzyl cyanide in the presence of sodium ethoxide to form cyanobenzylidene phthalide[108]:



Addition at Unsaturated Linkages

The sodium derivatives of certain nitriles with an active methylenic group condense with compounds with reactive unsaturated linkages. Thus, sodiocyanoacetic ethyl ester reacts with the ethyl ester of 4-methyl-2-butene-1-acid as follows[115]:

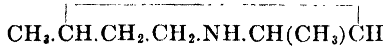
$$(CH_3)_2C:CH.COOC_2H_5 + CN.CH(Na).COOC_2H_5 \rightarrow (CH_3)_2C[CH(Na)COOC_2H_5].CH(CN).COOC_2H_5$$

Sodioethyl α-cyanopropionate, $CNC(CH_3)(Na).COOC_2H_5$, gives the methylated compound[116], $(CH_3)_2C[CH(Na)COOC_2H_5].C(CH_3)(CN).COOC_2H_5$. *Ethyl α-methylacrylate* forms with sodiocyanoacetic ethyl ester the compound[117], $C_2H_5OCOCH(CH_3).CH_2.CNa(CN).COOC_2H_5$. With *ethyl acrylate* the compound, $C_2H_5OCO.CNa(CN).CH_2.CH_2.COOC_2H_5$, forms[118].

Sodio ethyl cyanoacetate condensing with allyl cyanide forms β-methyl-γ-carbethoxyglutaronitrile, b.p.$_3$ = 160°, in 90% yield; similarly, sodio ethyl α-cyanopropionate, condensing with allyl cyanide, gives α,β-dimethyl-γ-carbethoxyglutaronitrile, b.p.$_3$ = 142°[234]. With ethyl crotonate, sodio ethyl cyanoacetate gives the cyanomethylglutaric ester, $EtOCOCH(CN)CH(CH_3).CH_2$-

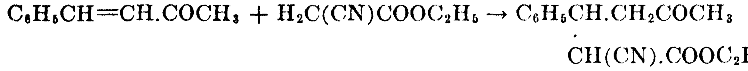
COOEt. Ethyl α-methylcrotonate similarly gives cyanodimethylglutaric diethy ester[300].

Ethylideneacetone, $CH_3CH:CH.COCH_3$, condenses with sodiocyanoacetic ester to $C_2H_5OCO.CH(CN).CH(CH_3).CH_2COCH_3$, and this on decarboxylation, followed by reduction, gives dimethylpiperidine[119].



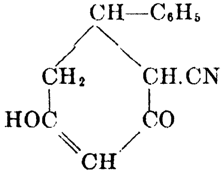
$$\overline{CH_3.CH.CH_2.CH_2.NH.CH(CH_3)CH_2}$$

Ethyl cyanoacetate condensing with *benzalacetone* in the presence of a small quantity of sodium ethoxide forms ethyl α-cyano-β-phenyl-γ-acetylbutyrate, b.p.$_{12}$ 203°:



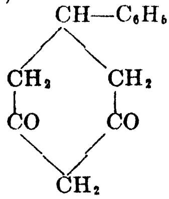
$$C_6H_5CH{=}CH.COCH_3 + H_2C(CN)COOC_2H_5 \rightarrow \begin{array}{l} C_6H_5CH.CH_2COCH_3 \\ \quad\quad\; CH(CN).COOC_2H_5 \end{array}$$

This compound, heated to boiling in alcoholic solution, gives cyanophenylhydroresorcinol,



(m.p. 180°)

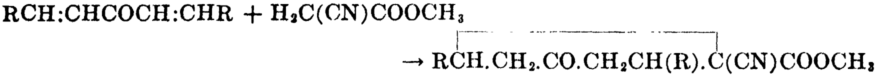
and phenylhydroresorcinol,



(m.p. 190°)

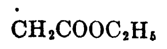
These products form directly from benzalacetone and ethyl cyanoacetate when the reaction is carried out in the presence of a large quantity of sodium ethoxide[238].

Methyl cyanoacetate has been condensed with *dibenzalacetone* and similar pentadienenes in the presence of sodium methylate to cyclohexanone derivatives[120]:



$$RCH:CHCOCH:CHR + H_2C(CN)COOCH_3 \rightarrow \overline{RCH.CH_2.CO.CH_2CH(R).C}(CN)COOCH_3$$

Sodio ethyl cyanoacetate condenses with *diethyl β-methylglutaconate*, $C_2H_5OCO.CH_2.C(CH_3):CH.COOC_2H_5$, forming principally the compound,



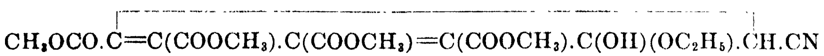
$$\begin{array}{l} C_2H_5OCO.CH_2.C(CH_3).CNa(CN)COOC_2H_5 \\ \quad\quad\quad\quad\quad CH_2COOC_2H_5 \end{array}$$

a certain amount of the compound[121] $C_2H_5OCO.CH_2.CH(CH_3).CH(COOC_2H_5)$-$CNa(CN).COOC_2H_5$ forming at the same time.

Methyl cyanoacetate condenses with *methyl glutaconate* in the presence of sodium methoxide forming $(CH_3OCOCH_2)_2CH.CH(CN)COOCH_3$, b.p.$_4$ = 185°.

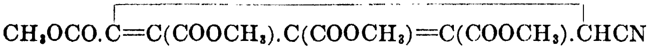
β-Methylglutaconic esters also condense with methyl cyanoacetate forming $(C_2H_5OCOCH_2)_2C(CH_3).CH(CN).COOCH_3$, b.p.$_4$ = 180–185°[239].

Ethyl cyanoacetate reacts with *methyl acetylenedicarboxylate* in ether solution and in the presence of pyridine and acetic acid forming



$$CH_3OCO.C{=}C(COOCH_3).C(COOCH_3){=}C(COOCH_3).C(OH)(OC_2H_5).CH.CN$$

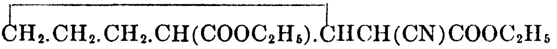
or



$$CH_3OCO.C{=}C(COOCH_3).C(COOCH_3){=}C(COOCH_3).CHCN$$

depending on the ratio of the weight of pyridine to that of acetic acid; the former when a 1:1 proportion is used, the latter when a 5.5:3 proportion is used[273].

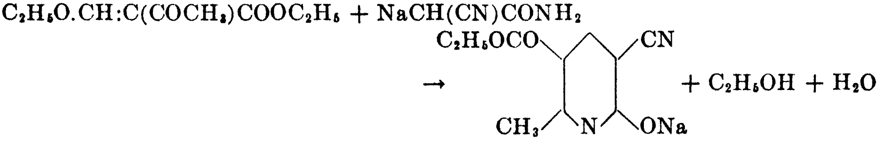
Ethyl Δ¹-cyclopentenecarboxylate reacts with sodio ethyl cyanoacetate to form mainly the ethyl ester of α-cyanocarbethoxy-1-cyclopentane-2-acetic acid,



$$CH_2.CH_2.CH_2.CH(COOC_2H_5).CHCH(CN)COOC_2H_5$$

The free acid is decarboxylated on distillation under vacuum to 1-carbethoxycyclopentane-2-acetonitrile[284]. Ethyl-Δ³-tetrahydro-*p*-toluate reacting successively with sodio ethyl cyanoacetate and β-chloropropionitrile gives 1-carbethoxy-4-methyl-α-(α-ethyl cyanoglutarate)-2, which, converted to the corresponding glutarate and condensed under the action of metallic sodium gives 1-keto-6-methyldecalin-4-carboxylic acid, prisms melting at 191°. 1-Carbethoxy-4-methylcyclohexane-2-α-cyanosuccinic ethyl ester is similarly obtained from ethyl tetrahydro-*p*-toluate, sodio ethyl cyanoacetate and ethyl bromoacetate, and 1-carbethoxy-4-methylcyclohexane-2-α′-methylcyanosuccinic ethyl ester from ethyl tetrahydro-*p*-toluate, sodio ethyl cyanoacetate and ethyl α-bromopropionate[285].

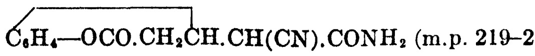
Hydroxy-β′-cyano-α-picoline-β-carboxylic ethyl ester has been obtained by the action of sodiocyanoacetamide on ethoxymethyleneacetylacetic ester[122]:



$C_2H_5O.CH{:}C(COCH_3)COOC_2H_5 + NaCH(CN)CONH_2$

The free acid heated at 130° with hydrochloric acid is converted to hydroxy-α-picoline, m.p. 157°.

Cyanoacetamide reacts with *coumarin* in the presence of pyridine forming 3,4-dihydrocoumarin-4-cyanoacetamide,



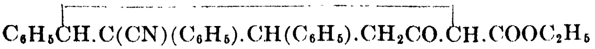
$$C_6H_4{-}OCO.CH_2CH.CH(CN).CONH_2$$ (m.p. 219–220°)

7-Methyl-, 6-nitro- and 6-amino- analogs of this compound have also been prepared from cyanoacetamide and the corresponding coumarins[240].

Benzyl cyanide condenses with *cinnamic esters* in the presence of sodium ethoxide, the methylenic group adding at the double bond[123]:

$$C_6H_5CH{:}CH.COOC_2H_5 + H_2C(CN)C_6H_5 \rightarrow C_6H_5CH.[CH(CN).C_6H_5].CH_2.COOC_2H_5$$

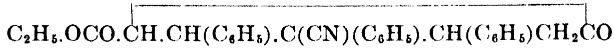
Several other products are formed simultaneously, thus, the compound,



$$C_6H_5CH.C(CN)(C_6H_5).CH(C_6H_5).CH_2CO.CH.COOC_2H_5$$

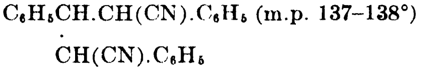
or an isomeric form has been isolated from the reaction product. The following are also formed:

$C_2H_5OCO.CH_2.CH(C_6H_5).C(CN)(C_6H_5).CH(C_6H_5).CH_2COOC_2H_5$, and



$$C_2H_5.OCO.CH.CH(C_6H_5).C(CN)(C_6H_5).CH(C_6H_5)CH_2CO$$

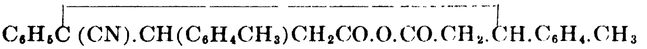
Benzyl cyanide in excess reacts with *benzaldehyde* to form *sym.*-triphenylglutaronitrile[124],



$$\begin{array}{l}C_6H_5CH.CH(CN).C_6H_5 \text{ (m.p. 137–138°)}\\ \quad\cdot\\ CH(CN).C_6H_5\end{array}$$

the compound, $C_6H_5CH{:}C(CN).C_6H_5$, forming first. The corresponding acid has been prepared from the nitrile by hydrolysis.

Benzyl cyanide, reacting with *ethyl-p-methylcinnamate*, $CH_3C_6H_4CH{:}$-$CHCOOC_2H_5$, in the presence of sodium ethoxide, forms sodium-*p*-tolyl-γ-phenyl-γ-cyanobutyrate, $CH_3C_6H_4CH(CH_2COONa)CH(CN)C_6H_5$; a small amount of the compound,



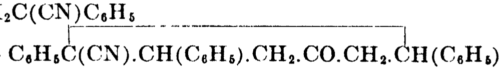
$$C_6H_5C\,(CN).CH(C_6H_4CH_3)CH_2CO.O.CO.CH_2.CH.C_6H_4.CH_3$$

also forming[125].

Benzyl cyanide reacts with *dicinnamylketone* in the presence of sodium alcoholate to form γ-cinnamoyl-α, β-diphenylbutyronitrile and 4-keto-1,2,6-triphenylcyclohexane nitrile[126]:

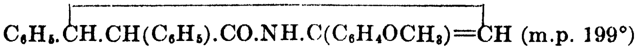
$$C_6H_5CH{:}CH.CO.CH{:}CH.C_6H_5 + H_2C(CN).C_6H_5 \rightarrow C_6H_5.CH(CN).CH(C_6H_5).CH_2.CO.CH{:}CH.C_6H_5$$

$$C_6H_5CH{:}CH.CO.CH{:}CH.C_6H_5 + H_2C(CN)C_6H_5$$



$$\rightarrow C_6H_5C(CN).CH(C_6H_5).CH_2.CO.CH_2.CH(C_6H_5)$$

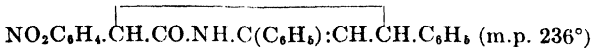
Benzyl cyanide reacts with *benzylidene-p-methoxyacetophenone*, $C_6H_5CH{:}CH_2.COC_6H_4OCH_3$, in the presence of sodium methoxide forming α,β-diphenyl-γ-(*p*-methoxybenzoyl)-butyronitrile[241], $C_6H_5CH(CN).CH(C_6H_5).CH_2.CO.C_6H_4OCH_3$, prisms melting at 116°. Hydrolyzed with hydrogen bromide in acetic acid solution, this gives 2-keto-3,4-diphenyl-6-(*p*-methoxyphenyl) tetrahydropyridine,



$$C_6H_5.CH.CH(C_6H_5).CO.NH.C(C_6H_4OCH_3){=}CH \text{ (m.p. 199°)}$$

Paranitrobenzyl cyanide gives α-*p*-nitrophenyl-β-phenyl-γ-(*p*-methoxybenzoyl)butyronitrile, m.p. 151°.

p-Nitrobenzyl cyanide condenses with *benzylideneacetophenone* in the presence of a trace of potassium hydroxide to two isomeric α-*p*-nitrophenyl-β-phenyl-γ-benzoylbutyronitriles[242], $NO_2.C_6H_4.CH(CN).CH(C_6H_5).CH_2COC_6H_5$, melting at 126° and 144°. The low melting compound is converted to the high melting isomer by hot alkalies. The high melting isomer is converted on heating with a solution of hydrobromic acid in acetic acid solution to 2-keto-3-nitrophenyl-4,6-diphenyltetrahydropyridine,

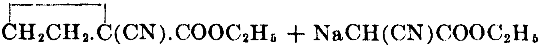


$NO_2C_6H_4.CH.CO.NH.C(C_6H_5):CH.CH.C_6H_5$ (m.p. 236°)

the low melting isomer subjected to the same treatment, gives the compound, $C_{23}H_{18}O_3N_2.2HBr$, m.p. 118–119°.

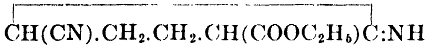
Condensation products have also been prepared from benzyl cyanide and *acrylonitrile*, β-phenylacrylonitrile and *p*-methoxyacrylonitrile; also from *p*-methoxy- and *m*-amino-benzyl cyanide and β-phenylacrylonitrile[127].

Cyanocarbethoxycyclopropane reacts with sodio ethyl cyanoacetate to form the ester of an open chain dicyanodicarboxylic acid,



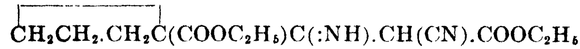
$$CH_2CH_2.C(CN).COOC_2H_5 + NaCH(CN)COOC_2H_5 \rightarrow C_2H_5OCO.CNa(CN).CH_2.CH_2CH(CN)COOC_2H_5$$

which has been condensed to



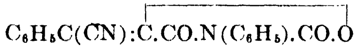
$CH(CN).CH_2.CH_2.CH(COOC_2H_5)C:NH$

The corresponding cyclobutane compound condenses with ethyl cyanoacetate to form the compound[128],



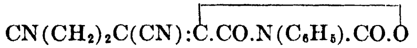
$CH_2CH_2.CH_2C(COOC_2H_5)C(:NH).CH(CN).COOC_2H_5$

Oxalphenylacetonitrile, $C_6H_5C(CN):C(OH).COOC_2H_5$, heated with phenyl *iso*cyanate gives the anile of 1-cyano-1-phenyl-*o*-carboxypropene-1-ol-2-oic-3-acid,



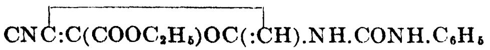
$C_6H_5C(CN):C.CO.N(C_6H_5).CO.O$

needles, m.p. 210°. The ethyl ester of hydroxyglutaric dinitrile, $CN(CH_2)_2.C(CN):C(OH).COOC_2H_5$, similarly gives with phenyl *iso*cyanate the anile of 3,5-dicyano-o-carboxypentene-2-ol-oic-1-acid,



$CN(CH_2)_2C(CN):C.CO.N(C_6H_5).CO.O$

prisms melting at 133°. β-Oxalsuccinic nitrile gives with phenyl *iso*cyanate the N-carbanilide of the ethyl ester of 5-amino-3-cyanofurfurane-2-carboxylic acid[129],



$CNC:C(COOC_2H_5)OC(:CH).NH.CONH.C_6H_5$

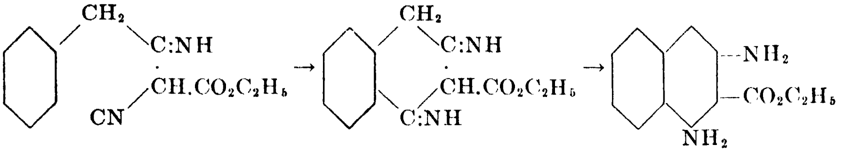
Condensation with Nitrile Groups

Sodium derivatives of nitriles containing an active methylene group may condense with nitrile groups to imino-compounds. Thus, these sodium derivatives react with benzonitrile to yield compounds of the type $C_6H_5C(:NH).CH(CN)X$, where X designates a strongly negative radical[130].

Sodio ethyl cyanoacetate condenses with *phenylacetonitrile* in this manner:

$$C_6H_5.CH_2CN + NaCH(CN).COOC_2H_5 \rightarrow C_6H_5.CH_2.C(:NH).CH(CN).COOC_2H_5$$

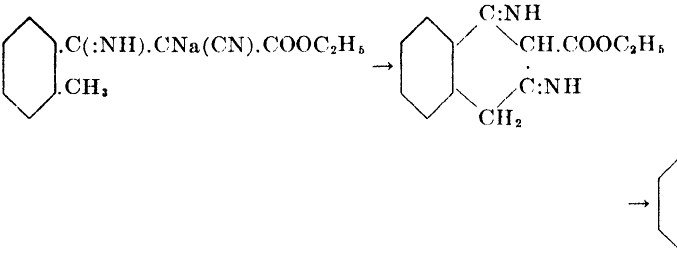
When treated with cold concentrated sulfuric acid, this compound undergoes the following changes:



The keto compound, $C_6H_5.CH_2.CO.CH(CN)CO_2C_2H_5$, does not undergo this cyclization.

Condensation products, $CH_3C_6H_4.CH_2.C(:NH).CH(CN).CO_2C_2H_5$, have also been obtained from tolylacetonitriles, but of these only the *meta* isomer gives a good yield of cyclic compound.

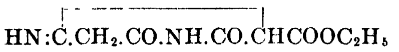
The condensation product of *o*-tolunitrile with sodium ethyl cyanoacetate also condenses under the action of concentrated sulfuric acid to a diamino compound[130]:



Ethyl cyanoacetate condenses with its sodium compound in the same manner[131]:

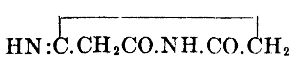
$$C_2H_5OCO.CH_2.CN + CNCH(Na).COOC_2H_5$$
$$\rightarrow C_2H_5OCO.CH_2.C(:NH).CNa(CN)COOC_2H_5$$

One ester group may be saponified by heating with sodium carbonate solution; the acid obtained is $HOCO.CH_2.C(:NH).CH(CN).COOC_2H_5$. Heated at 144°, this may be transformed to:



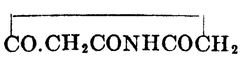
$$HN:\overline{C.CH_2.CO.NH.CO.C}HCOOC_2H_5$$

which may be decarboxylated by heating with sodium hydroxide to:



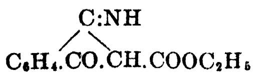
$$HN:\overline{C.CH_2CO.NH.CO.C}H_2$$

By treatment with hot concentrated hydrochloric acid, this may be converted to the keto-compound:



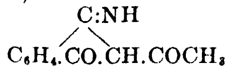
$$\overline{C}O.CH_2CONHCO\overline{C}H_2$$

o-Cyanobenzoyl chloride reacts in the cold with sodium ethyl acetoacetate forming $C_6H_4(CN).COCH(COCH_3).COOC_2H_5$; this compound has been condensed to



$$C_6H_4\overbrace{.CO.CH}^{C:NH}.COOC_2H_5$$

A similar condensation product,



$$C_6H_4(CO)(C{:}NH)CH.COCH_3$$

has been obtained from cyanobenzoyl chloride and sodium acetylacetone[63].

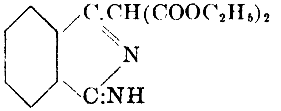
Phenylacetonitrile condenses with itself in the presence of sodium ethoxide:

$$2C_6H_5CH_2CN \rightarrow C_6H_5CH_2C({:}NH).CH(CN).C_6H_5$$

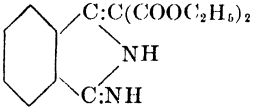
A certain amount of cyanobenzyline, the trimer of phenylacetonitrile, also forms simultaneously. The keto-compound, $C_6H_5.CH_2.CO.CH(CN).C_6H_5$, is obtained by the hydrolysis of the imino-compound. The iminonitrile may be cyclized with concentrated sulfuric acid to 2,4-diamino-3-phenylnaphthalene[132].

While the type of condensation of nitriles under discussion is a general one, certain nitriles, such as *o*-toluonitrile, react slowly or not at all, due to the factor of steric hindrance.

Phthalonitrile in warm alcoholic solution condenses with sodium compounds of phenylacetonitrile, ethyl cyanoacetate and ethyl malonate. The reaction is exothermic. The product of the reaction with sodium ethyl malonate is the sodium derivative of the *iso*indole:



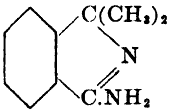
or



The reaction with sodium cyanoacetic ethyl ester and with phenylacetonitrile follows a similar course giving respectively a 70% yield of 3-cyanocarbethoxymethylene phthalimidine, m.p. 170°, and an 87% yield of 1-imino-3-cyanobenzylidenephthalimidine, m.p. 207–208.

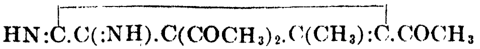
Sodium ethyl acetoacetate and sodium ethyl methylmalonate do not combine with phthalonitrile to any great extent[133].

Methyl lithium reacts with *phthalonitrile* to form, after hydrolysis, 1-amino-3,3-dimethyl*iso*indole:



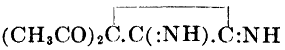
Methylmagnesium iodide reacts in a similar manner[134].

Cyanogen reacts in alcoholic solution with sodio ethyl malonic ester to form the compounds: $(C_2H_5OCO)_2C(Na).C({:}NH).CN$ and $(C_2H_5OCO)_2C(Na)C({:}NH).$-$C({:}NH).CNa(COOC_2H_5)_2$. Sodium ethyl acetoacetate and acetylacetone also form similar cyanoketimines and diketimines. The cyanoketimines are decomposed to a monocyano-compound and alkali cyanide by treatment with alkali. The diketimine obtained with sodium acetylacetone may be condensed to the ring compound:



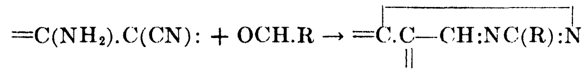
$$HN{:}C.C({:}NH).C(COCH_3)_2.C(CH_3){:}C.COCH_3$$

The cyanoketimine condenses to[135]



$$(CH_3CO)_2C.C(:NH).C:NH$$

Certain *ortho*-aminonitriles have been condensed with aldehydes in the presence of acids to dihydropyrimidines,



$$=C(NH_2).C(CN): + OCH.R \rightarrow =C.C{-}CH:NC(R):N$$

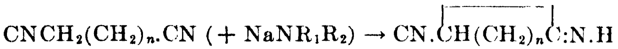
From these compounds, dyes or dye intermediates and some medicinal chemicals have been obtained by dehydrogenation or halogenation[136].

Cyclization of Nitriles

When nitriles, RCH_2CN, are treated with the sodium compound of a secondary aromatic aliphatic amine, $NaNR_1R_2$, one α-hydrogen in the nitrile molecule is replaced with sodium:

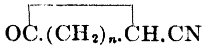
$$RCH_2CN + NaNR_1R_2 \rightarrow RCH(Na).CN + HNR_1R_2$$

The reaction takes place also with other alkali metal compounds of the secondary amine. When two nitrile groups are present in the molecule, internal condensation takes place and a cyclic iminonitrile forms:



$$CNCH_2(CH_2)_n.CN\ (+ NaNR_1R_2) \rightarrow CN.CH(CH_2)_nC:N.H$$

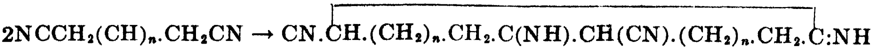
The transformation takes place also when alkaline-earth metal or magnesium amides are used. On hydrolysis these compounds form cyclic ketones[137],



$$OC.(CH_2)_n.CH.CN$$

Ziegler showed that good yields of the cyclic compounds may best be obtained by carrying out the reaction in dilute solution. He obtained yields approaching 100% from nitriles with 5-, 6- and 7-carbon chains. A fair yield of cyclic product was obtained from the nitrile with 8-carbon chain, but nitriles with 9 to 12 carbon atoms gave low yields; then a maximum in yield was reached for the nitrile with 18 carbons. In general, nitriles with an even number of carbon atoms gave higher yields than those with an odd number. Ziegler and Hechelhammer prepared cyclic ketones from dinitriles with 21 to 34 carbon atoms in yields ranging from 65 to over 86%[138].

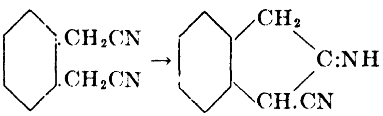
Cyclization may also take place between two molecules of a dinitrile to form a cyclic dicyanodiimino compound:



$$2NCCH_2(CH)_n.CH_2CN \rightarrow CN.CH.(CH_2)_n.CH_2.C(NH).CH(CN).(CH_2)_n.CH_2.C:NH$$

Compounds of this type have been obtained from sebacic nitrile, 1,9-dicyanononane, 1,10-dicyanodecane, 1,11-dicyanoundecane, 1,12-dicyanododecane. On hydrolysis these compounds are transformed to cyclic dicyanodiketones[139].

Cyclization takes place also in the case of dinitriles of the aromatic series. Thus, *o*-dicyanomethylbenzene condenses quantitatively in the presence of sodium ethoxide to *β*-imino-*α*-cyanohydrindene:



The compound is converted by hydrolysis to the corresponding ketone[140]. Attempts to bring about the cyclization of *m*-dicyanoethylbenzene, $C_6H_4(CH_2\text{-}CH_2CN)_2$, and *m*-dicyanopropylbenzene, $C_6H_4(CH_2.CH_2.CH_2CN)_2$, have failed[141].

ω-ω′-Dicyano-2,2′-ditolyl, $CNCH_2.C_6H_4.C_6H_4.CH_2CN$, has been cyclized to 1-imino-2-cyano-3,5-dibenzo-$\Delta^{3:5}$-cycloheptadiene,

$$\mathrm{CN\overline{CH.C_6H_4.C_6H_4.C}:NH}$$

By hydrolysis with cold sulfuric acid, the corresponding iminocarboxylic acid has been obtained; by hydrolysis with hot dilute sulfuric acid, 3:5-dibenzo-$\Delta^{3.5}$-cycloheptadiene-1-one has been prepared[142]. Dicyanohexyl ethers of resorcinol and hydroquinone have been successfully cyclized:

$$\mathrm{CNCH_2(CH_2)_4CH_2OC_6H_4OCH_2(CH_2)_4CH_2CN}$$

$$\rightarrow \mathrm{CN\overline{CH(CH_2)_4.CH_2OC_6H_4OCH_2(CH_2)_4CH_2C}NH}$$

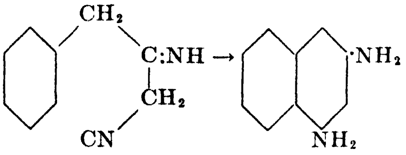
The corresponding keto compounds have been obtained by hydrolysis of the imino compounds[141].

Thorpe cyclized adiponitrile to imino-2-cyanocyclopentane by heating with sodium ethoxide:

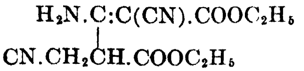
$$\mathrm{CN.CH_2(CH_2)_2CH_2CN} \rightarrow \mathrm{\overline{CH_2.(CH_2)_2.CH(CN).C}:NH}$$

α-Carbethoxyadiponitrile has been similarly condensed to imino-2-cyano-5-carbethoxycyclopentane[143].

Ring closure through the transfer of a mobile hydrogen atom to a nitrile group is observed also in the case of mononitriles. Thus, iminophenylbutyronitrile may be condensed to 1:3-naphthalenediamine[144]:

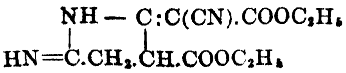


The aminonitrile,



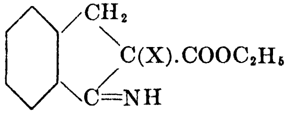
$$\begin{array}{l} \mathrm{\quad H_2N.C{:}C(CN).COOC_2H_5} \\ \mathrm{CN.CH_2\overset{|}{C}H.COOC_2H_5} \end{array}$$

has been condensed to:



$$\begin{array}{l} \mathrm{\qquad NH - C{:}C(CN).COOC_2H_5} \\ \mathrm{HN{=}\overset{|}{C}.CH_2.\overset{|}{C}H.COOC_2H_5} \end{array}$$

The product of the interaction of *o*-cyanobenzyl chloride and the sodio compound, $CHNa(X).COOC_2H_5$, in which X is an acetyl or other similar negative group, namely $C_6H_5(CN).CH_2CH(X).COOC_2H_5$, has been condensed to:



Condensations with Nitroso and Other Reactive Nitrogen Groups

Benzyl cyanide reacts with nitroso compounds to form azomethinphenyls:

$$C_6H_5CH_2CN + ON.R \rightarrow C_6H_5C(CN):N.R + H_2O$$

The compound, $C_6H_5C(CN):N(:O).R$, forms simultaneously[145].

Nuclearly substituted benzyl cyanides react in a similar manner. Thus, *p*-nitrosodimethylaniline has been condensed in alcoholic solution in the presence of sodium hydroxide with *m*-methyl-, 2,4-dimethyl- and *o*-cyanophenylacetonitriles. 2-Methylnaphthylacetonitrile also reacts normally with *p*-nitrosoaniline. 2,4,6- and 2,6,4-trimethylphenylacetonitriles fail to react, probably because of steric hindrance due to the substituents[274].

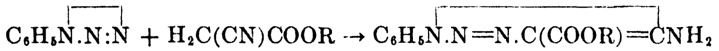
Malononitrile, cyanoacetic acid and *cyanoacetamide* react in a similar manner with nitroso compounds.

Monosubstituted cyanoacetic esters react with alkylnitrites in anhydrous ether in the presence of sodium ethoxide to form pyruvonitrile oximes[149]:

$$R.CH(CN).COOC_2H_5 + ONO.C_5H_{11} \rightarrow RC(CN):NOC_5H_{11} + CO_2 + C_2H_5OH$$

Aromatic diazonium compounds react with this type of esters to form pyruvonitrile hydrazones[149], $R.C(CN):N.NAr$.

Diazobenzolimide and other esters of hydrazoic acid react with cyanoacetic esters giving 5-amino-1,2,3-triazoles[289]:



$$C_6H_5N.N:N + H_2C(CN)COOR \rightarrow C_6H_5N.N{=}N.C(COOR){=}CNH_2$$

Sachs obtained cyanoazomethinphenyl, $C_6H_5C(CN):N.C_6H_5$, m.p. 72°, by this reaction from benzyl cyanide and nitrosobenzene. A compound melting at 141° formed at the same time, which was later proved to be a nitron[146], $C_6H_5C(CN):N(:O).C_6H_5$. Barrow and Thorneycroft[147] isolated two isomeric forms of this compound. The probable mechanism of nitron formation is as follows:

$$C_6H_5.CH_2CN + ON.C_6H_5 \rightarrow C_6H_5CH(CN).N(OH).C_6H_5$$

$$2C_6H_5CH(CN).N(OH).C_6H_5 + ON.C_6H_5 \rightarrow 2C_6H_5C(CN):NO.C_6H_5 + H_2O + H_2NC_6H_5$$

By using an excess of benzyl cyanide, almost pure azomethin, melting at 72°, may be obtained[148]. In addition to the phenyl-compound, the following cyanoazomethinphenyls have been prepared: *p*-nitrophenyl-, m.p. 140°; *p*-hydroxyphenyl-, m.p. 146°; *p*-acetaminophenyl-, m.p. 146°; naphthyl-, m.p. 103°.

Malonic nitrile, reacting with amyl nitrite in absolute alcoholic solution in the presence of sodium ethoxide, forms the compound $HON:C(CN)C(OC_2H_5)(OH)$-

NH_2; this, on treatment with hydrochloric acid, is converted to ethyl *iso*nitrosocyanoacetate[150].

Zimmermann prepared benzocyanoaldoxime, $C_6H_5C(CN){:}NOH$, m.p. 129°, by condensing *benzyl cyanide* with *amyl nitrite* in the presence of sodium ethoxide and subsequently decompositing the resulting sodium compound with dilute sulfuric acid. By the same method he also prepared *p*-nitrobenzo-, *p*-chlorobenzo- and *o*-chlorobenzo-cyanoaldoximes. These compounds are converted by nitrous acid to ketonitriles[151], R.CO.CN.

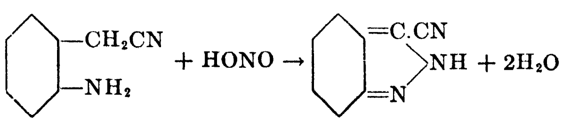
Benzyl cyanide reacts with *ethyl* or *amyl nitrate* in the presence of sodium ethoxide forming the sodium compound of phenyl*iso*nitroacetonitrile[152], C_6H_5-$C(CN){:}NOONa$. Ethyl cyanoacetate does not give this reaction[243].

Ortho- and *para*-bromobenzyl cyanides[153], methylbenzyl cyanides and α- and β-naphthylmethyl cyanides[154] react in the same manner as benzyl cyanide, the *p*-bromo compound reacting less readily than the *o*-compound. The free nitro-compounds, $RCH(CN)NO_2$, have been obtained by the exchange of hydrogen for sodium. The bromophenyl compounds have been brominated to BrC_6H_4-$CBr(CN).NO_2$; these are converted to BrC_6H_4COCN on heating to 50–60°.

Sulfonylacetonitriles, RSO_2CH_2CN, condense with amyl nitrite in the presence of sodium ethoxide to oximes[155], $RSO_2C({:}NOH)CN$. The oxime group is substituted by two bromine atoms to give $RSO_2CBr_2.CN$ when these compounds are treated with bromine water. Iodine in potassium iodide solution is without action on the oximes. Attempts to convert the oxime or the dibromo-compound to a ketone have been unsuccessful[156]. The oxime group has the character of an acid, the hydrogen being replaceable by metals and organic radicals[157].

Ethyl *iso*nitrosocyanoacetate may be obtained by pouring a mixture of *ethyl cyanoacetate* and an aqueous solution of *sodium nitrite* into acetic acid. *Iso*nitrosocyanoacetamide may be prepared in the same manner from cyanoacetamide. *Iso*-nitroso derivatives have also been prepared from methyl cyanoacetate and cyanoacetanilide[158].

Nitrous acid reacting with *o*-aminobenzyl cyanide gives *indazole-3-nitrile*, m.p. 140°[290]:



Diisonitraminobenzyl cyanide, $C_6H_5C(CN)(N_2O_2H)_2$, in the form of its sodium salt, results when an alcoholic solution of benzyl cyanide containing two molecular equivalents of sodium ethoxide is saturated with nitric oxide[291].

Cyanoacetophenone gives with *hydroxylamine* a compound of the empirical formula: $C_9H_8N_2O$; Rothenburg[159] believed the compound has the structure:

$$C_6H_5C{:}NO.C(NH)CH_2 \text{ or } C_6H_5C{:}NO.C(NH_2){:}CH$$

Reaction with Diazochlorides. Diazochlorides react with ethyl cyanoacetate and other cyanoacetic esters in the presence of sodium ethoxide forming ethyl azocyanoacetates:

$$C_2H_5OCOCH(Na)CN + Cl.N{:}N.R \rightarrow NaCl + C_2H_5OCOCH(CN)N{:}NR \text{ or } C_2H_5OCO.C(CN){:}N.NHR$$

The two isomeric modifications are formed simultaneously. Ethyl phenyl-, *o*- and *p*-tolyl-, *m*-xylyl-, *pseudo*cumyl-, carboxy phenyl diazocyanoacetates and methyl *p*-tolyldiazocyanoacetate, have been prepared among others[160]. The compounds may also be prepared from the diazo compounds and cyanoacetic ester in the presence of sodium acetate. Similar products may also be obtained from malononitrile[161]. Tetrazoic derivatives, such as $C_2H_5OCO.C(CN){:}N.N(R).C_6H_4N(R).$-$N{:}C(CN)COOC_2H_5$, in which R is H, CH_3-,C_2H_5- and $C_6H_5.CO$-, have been prepared by Favrel[162].

Substituted ethyl cyanoacetates, such as $CH_3CH(CN)COOC_2H_5$ and C_2H_5-$CH(CN)COOC_2H_5$ react with aromatic diazochlorides forming compounds of the type: $RNHN{:}C(CN)CH_3$, $RNH.N{:}C(CN)C_2H_5$ with elimination of carbon dioxide and alcohol[163]. Acetylated cyanoacetates, $CH_3CO.CH(CN)COOR$, form diazo-compounds, $RNH.N{:}C(CN)COOR$, with the elimination of acetic acid[164].

α-Sulfonylacetonitriles, $RSO_2.CH_2CN$, react with diazochlorides, $R'N_2Cl$, in alcoholic solution in the presence of sodium acetate to form hydrazones[165], RSO_2-$C(CN){:}N.NHR'$. α-Sulfonyl propionitrile, reacting with diazochlorides, gives true diazo-compounds[166].

Halogenation of Active Methylenic Groups

Malononitrile may be directly brominated to a mono- or dibromide:

$$CN.CH_2.CN + Br_2 \rightarrow CNCHBr.CN$$
$$CNCHBrCN + Br_2 \rightarrow CN.CBr_2.CN^*$$

The dibromide originally prepared was found to be unstable in ether solution.

The dibromide reacts with malononitrile to form the monobromide to a large extent. The dibromide forms complex salts with metallic bromides, $XBr.4CBr_2(CN_2)$, X=K, Na, Li, NH_4. The dibromide may be isolated from these complex salts by sublimation under vacuum. Copper bromide gives a complex salt from which cyanodibromoacetamide has been obtained by sublimation.

Malononitrile is regenerated from monobromomalononitrile by the action of hydriodic acid:

$$CN.CHBr.CN + 2HI \rightarrow CN.CH_2.CN + HBr + 2I$$

This reaction may serve as a basis for the estimation of monobromomalonitrile[167].

Monoazidomalononitrile has been prepared from dibromomalononitrile; a dicyanoazide has also been prepared similarly[169].

Malononitrile may also be chlorinated directly. The monochloride boils without decomposition at 97° under atmospheric pressure. The dichloride adds two molecules of chlorine to form a tetrachloride[170]. While benzyl cyanide forms a monochloro compound, *p*-nitrobenzyl cyanide gives a dichloro compound, NO_2-$C_6H_4CCl_2.CN$, yellow oil boiling at 149–149.5° under 0.6 mm pressure, hydrolyzed by strong acids to *p*-nitrobenzoic[174,244].

Halogens replace one hydrogen atom in the side chain in ***benzyl cyanide*** at elevated temperatures or in the presence of catalysts[171]. Benzyl cyanide may be brominated in chloroform solution in the cold in the presence of iodine to phenylbromoacetonitrile. Steinkopf carried out the bromination at 105° with bromine vapor under strong illumination; the compound was purified by distillation under vacuum. The pure compound melts at 25.4°[172]. Phenylbromoacetonitrile treated with metallic mercury forms the addition compound $C_6H_5CH(HgBr)CN$, colorless crystals melting at 157°, which is readily converted to dicyanodibenzyl[245], $C_6H_5CH(CN).CH(CN)C_6H_5$.

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* A small amount of dibromosuccinonitrile, m.p. 123–124° also forms; this was mistaken by Nef and Hesse[168] for dibromomalononitrile.

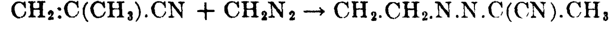
Phenylchloroacetonitrile, $C_6H_5CH(Cl)CN$, gives with sodium ethoxide in alcoholic solution dicyanostilbene[173], $C_6H_5C(CN){:}C(CN)C_6H_5$, m.p. 158°. The same compound is also obtained by heating benzyl cyanide with bromine at 160 to 180°[277]. On long boiling with alcoholic caustic, diphenylmaleic anhydride is obtained. Reacting with sodium sulfide, phenylchloroacetonitrile gives $S(CH(CN)C_6H_5)_2$; with sodium thiosulfate phenylmercaptoacetonitrile, $C_6H_5CH(SH)CN$, m.p. 101°, is obtained; ammonium thiocyanate gives phenylthiocyanoacetonitrile, m.p. 62–63°[246]. Heated with metallic copper, phenylchloroacetonitrile forms diphenylsuccinonitrile, m.p. 238–239°[247]. Dicyanostilbene also forms by passing diphenylsuccinonitrile over pelladium at 230–250° under 100–110 mm pressure[248].

Dichlorosulfonylacetonitriles are obtained by the chlorination of unsubstituted *sulfonyl acetonitriles*, RSO_2CH_2CN, with "nascent" chlorine generated by adding bleaching powder to an acetic acid solution of the nitrile. *Phenylsulfonylacetonitrile* may be directly chlorinated with dry chlorine. Iodine in potassium iodide solution is without action on the methylenic group of the sulfonylacetonitriles[175].

Sulfur monochloride reacts with phenylacetonitrile very slowly in the cold. Phenyl mono- and dichloroacetonitriles and diphenylmalenonitrile, m.p. 159–160°, are the products of the reaction. By refluxing phenylacetonitrile with two molecular equivalents of sulfur monochloride for forty hours, diphenyldichlorosuccinonitrile, m.p. 189–190°, may be obtained in approximately 40% yield[176].

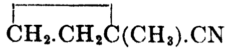
Miscellaneous Reactions

Diazomethane combines with *α-methylacrylonitrile* as follows:



$$CH_2{:}C(CH_3).CN + CH_2N_2 \rightarrow CH_2.CH_2.N.N.C(CN).CH_3$$

The resulting compound decomposes, on heating, to 1-methylcyclopropane cyanide,



$$CH_2.CH_2C(CH_3).CN$$

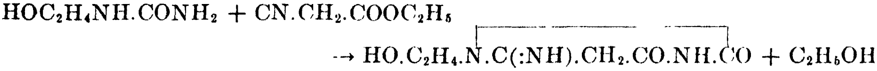
and nitrogen. A small amount of ethylenic nitrile also forms[177].

Nitriles condense with thioamides according to the equation:

$$R_1.CN + H_2NCS.R_2 \rightarrow R_1C({:}NH).N{:}C(SH).R_2$$

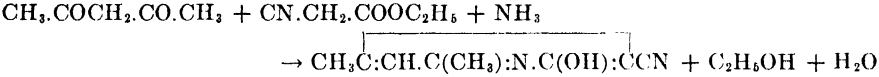
Cyanoacetic acid, reacting with *methyl cyanamide* in ethereal solution, forms cyanoacetylmethylurea, $CH_3NH.CO.NH.CO.CH_2.CN$, and methylurea cyanoacetate[178]. In the presence of acetic anhydride it reacts with *urethane* to form cyanoacetyl urethane[179], $C_2H_5OCO.NH.CO.CH_2CN$. Under the same conditions, cyanoacetyl urea forms from cyanoacetic acid and *urea*[180]. The reaction proceeds similarly when phosphorus oxychloride is used instead of acetic anhydride[181]. With *sym.*-dimethylurea in pyridine solution and in the presence of phosphorus oxychloride, 1,3-dimethyl-4-amino-2.6-dihydroxypyrimidine forms[182].

Esters of cyanoacetic acid react with substituted ureas in the cold in the presence of sodium ethoxide or magnesium methoxide to form substituted cyanoacetylureas; at a higher temperature 4-iminobarbituric acid derivatives form. Cyclohexylidene-, benzylidene-, dibenzyl- and ethylcyclohexenyl cyanoacetylureas and 4-imino*iso*propyl-, -diallyl- and -cyclohexenyl-barbituric acids have been prepared[249]. *Ethyl cyanoacetate* reacts with *β-hydroxyethylurea* in the presence of sodium ethoxide to form 1-(β-hydroxyethyl)-1,6-iminobarbituric acid:



$$HOC_2H_4NH.CONH_2 + CN.CH_2.COOC_2H_5 \rightarrow HO.C_2H_4.N.C(:NH).CH_2.CO.NH.CO + C_2H_5OH$$

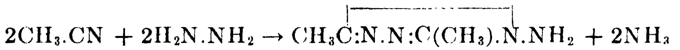
Ethyl cyanoacetate condenses with *acetylacetone* and ammonia to 2-hydroxy-3-cyano-4,6-dimethylpyridine[183]:



$$CH_3.COCH_2.CO.CH_3 + CN.CH_2.COOC_2H_5 + NH_3 \rightarrow CH_3C{:}CH.C(CH_3){:}N.C(OH){:}CCN + C_2H_5OH + H_2O$$

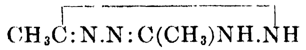
Malononitrile reacts with *hydrofuramide* in alcoholic solution forming $(CN)_2$-$CH.CH{=}CH.CH{=}C(OH).CH{=}C(CN)_2$, a compound of deep red color. This substance forms also when ammonia is added to an alcoholic solution of furfural and malononitrile. Cyanoacetamide gives a similar compound[250].

Acetonitrile combines with *hydrazine hydrate* on heating in sealed tubes to 150° to form C-dimethyl-N-aminotriazole:



$$2CH_3.CN + 2H_2N.NH_2 \rightarrow CH_3C{:}N.N{:}C(CH_3).N.NH_2 + 2NH_3$$

With anhydrous hydrazine the isomeric dimethyltetrazole



$$CH_3C{:}N.N{:}C(CH_3)NH.NH$$

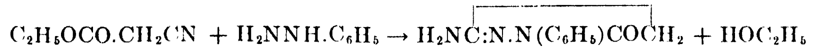
is obtained. Benzonitrile reacts in a similar manner[184].

Cyanoacetic azide, $CNCH_2CON_3$, which is obtained by diazotization of the corresponding hydrazide $CNCH_2CONHNH_2$ with nitrous acid, is readily converted with boiling alcohol to the urethane $CN.CH_2.NH.COOC_2H_5$ and this on treatment with boiling concentrated hydrochloric acid gives the aminoacid $HOCO.CH_2NH_2$. This method, which was originated by Darapsky[275], is also applicable in the case of substituted cyanoacetates and has been used for the preparation of a number of *amino acids*, among others valine, phenylalanine and tyrosine[276].

Ethyl α-cyanoacetoacetate forms an addition compound with cold phenylhydrazine. This compound decomposes smoothly when heated to 100° to ethyl cyanoacetate and β-acetylphenylhydrazine[185]:

$$CH_3CO.CH(CN).COOC_2H_5.2H_2N.NHC_6H_5 \rightarrow C_6H_5NH.NH_2 + CNCH_2COOC_2H_5 + CH_3CO.NH.NH.C_6H_5$$

Conrad and Zart[186] treated *ethyl cyanoacetate* with *phenylhydrazine* in the presence of sodium ethoxide and obtained a colorless compound of the empirical formula $C_9H_9N_3O$, melting at 219°. Weissberger and Porter have shown that the compound is 1-phenyl-3-amino-5-pyrazolone, formed according to the equation:



$$C_2H_5OCO.CH_2CN + H_2NNH.C_6H_5 \rightarrow H_2NC{:}N.N(C_6H_5)COCH_2 + HOC_2H_5$$

These authors prepared numerous derivatives of 3-amino-5-pyrazolones by this reaction, by the use of various substituted hydrazines, $R.NH.NH_2$. The yield of pyrazolone was found to vary according to the substituent. Thus, for R = $m.CH_3C_6H_4$, m-ClC_6H_4, $p.CH_3OC_6H_4$, p-sulfanylphenyl-, 3-pyridyl, 4-pyridyl and 2-pyridyl the yields were respectively 10, 64, 16.5, 2, 17, 5 and 30%[301].

Weissberger and co-workers arrived at these compounds by another route; namely, through the interaction of the ethyl imino ether, $EtOC(NH).CH_2COOEt$, and phenylhydrazine, and cyclization of the resulting ethyl β-hydrazino-β-imino propionate[302].

Hydrobenzamide, $C_6H_5CH{:}N.CH(C_6H_5)N{:}CH.C_6H_5$, condenses with *malononitrile* to form the compound $C_6H_5CH{:}N.CH(C_6H_5)NH.CH[CH(CN)_2].C_6H_5$, m.p. 142°. A similar compound also forms with cyanoacetamide, melting at 158°. Cyanoacetic acid does not react with hydrobenzamide. p-Methylhydrobenzamide reacts in the same manner as hydrobenzamide[251].

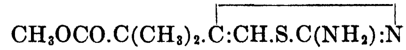
Cyanoacetic acid reacts with *triphenylcarbinol* to form triphenylpropionitrile[187]:

$$(C_6H_5)_3.COH + CH_2(CN).COOH \rightarrow (C_6H_5)_3C.CH_2CN + H_2O + CO_2$$

The compound exists in two isomeric forms, melting at 140° and 211°.

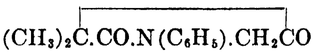
Ethyl cyanoacetate reacting with *quinone* in solution in concentrated ammonia forms a dark, purplish-red compound of the empirical formula $C_{16}H_{16}O_6N_2$, m.p. 278–278.5°; malononitrile gives a tan compound $C_{12}H_6O_2N_4$, cyanoacetamide gives black needles, both melting above 350°[280].

Cyanodimethylacetoacetic methyl ester, $CNCH_2COC(CH_3)_2COOCH_3$, reacts with thiourea forming aminothiazyl*iso*butyric methyl ester,



$$CH_3OCO.C(CH_3)_2.C{:}CH.S.C(NH_2){:}N$$

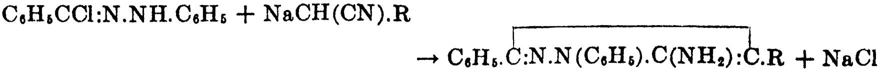
colorless leaflets, melting at 166°; with aniline, the compound,



$$(CH_3)_2C.CO.N(C_6H_5).CH_2CO$$

forms. The cyano-ester is made through the reaction of an alkaline cyanide with methyl bromodimethylacetoacetate[188].

Sodium derivatives of *nitriles*, $CN.CH_2R$, R representing the groups CN, $CONH_2$, CONH.Me, react with chlorobenzal phenylhydrazone, $C_6H_5CCl{:}N.NH.C_6H_5$, to form 5-amino-1,3-diphenylpyrazole-4-R[189]:

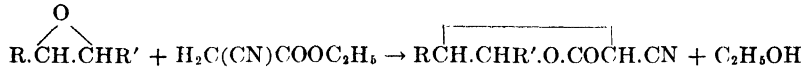


$$C_6H_5CCl{:}N.NH.C_6H_5 + NaCH(CN).R \rightarrow C_6H_5.C{:}N.N(C_6H_5).C(NH_2){:}C.R + NaCl$$

The 4-cyano-compound melts at 168°, the carboxyamido-compound at 186–187° and the carboxymethylamido-compound at 153°.

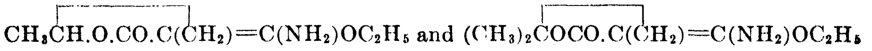
Benzoyl chloride reacts with monosodium malonitrile, forming a compound of unknown structure melting at 126–127°.

Ethyl cyanoacetate reacting with *alkene oxides* in the presence of one molecular equivalent of sodium ethoxide gives α-cyanolactones:



$$R.CH.CHR' + H_2C(CN)COOC_2H_5 \rightarrow RCH.CHR'.O.COCH.CN + C_2H_5OH$$

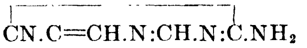
Such lactones have been made from propylene, *iso*butylene and cyclohexene oxides. Crystalline enamines, probably



$$CH_3CH.O.CO.C(CH_2)=C(NH_2)OC_2H_5 \text{ and } (CH_3)_2COCO.C(CH_2)=C(NH_2)OC_2H_5$$

have been obtained from propylene- and *iso*butylene oxides upon using 1/10 molal sodium ethoxide[292].

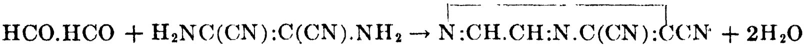
Formamidine and malononitrile condense to give 4-amino-5-cyanopyrimidine,



$$CN.C=CH.N:CH.N:C.NH_2$$

Other amidines react similarly forming derivatives of 4-amino-5-cyanopyrimidine. Aminomethylene or substituted aminomethylene derivatives appear to be the first products of the reaction. The more stable amidines such as benzamidine tend to give pyrimidines more readily. Aminomethylene type condensation takes place between formamidine and ethyl cyanoacetate, but a compound $C_9H_9O_3N_3$ has also been identified in the product of the reaction. This is probably a pyrimidine derivative[293].

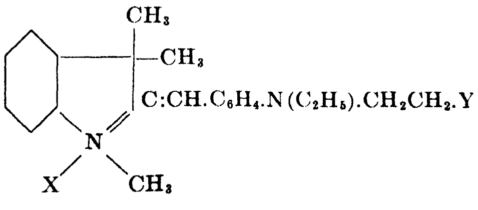
Diaminoethylene dinitrile (polymer of hydrocyanic acid) may be condensed with compounds containing the dicarbonyl group, —CO.CO—, or the chlorocarbonyl group, =C.Cl.CO—, to form pyrazine-2,3-dinitriles:



$$HCO.HCO + H_2NC(CN):C(CN).NH_2 \rightarrow N:CH.CH:N.C(CN):CCN + 2H_2O$$

From these compounds, dyes or pigments are obtained by heating alone or in the presence of cuprous bromide and pyridine[190].

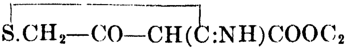
β-Aminonitriles, $R_1R_2N.CH_2CH_2CN$, condense with certain aldehydic compounds to form dyes of the general formula[191]:



Allyl cyanide combines with allyl alcohol to form an addition compound, $C_3H_5CN.C_3H_5OH$. A similar reaction also takes place with ethyl alcohol[192].

Chloracetylcyanoacetic ester, $Cl.CH_2.COCH(CN).COOC_2H_5$, reacts with potassium acid sulfide to form the mercaptan of acetylcyanoacetic ester and

thio-bis-acetylcyanoacetic ester, $S[CH_2.COCH(CN).COOC_2H_5]_2$. The mercaptan which melts at 200° probably exists in the tautomeric form[193]:



$$\overline{S.CH_2—CO—CH(C}:NH)COOC_2H_5$$

Benzoylmethylphenylacetonitrile, $C_6H_5COCH_2CH(Ph)CN$, reacting with *formamide*, gives 5-amino-2,4-diphenylpyrrole. The first stage in the reaction appears to be the formation of (iminomethyl)-benzoylmethylphenylacetonitrile, which then condenses with an additional molecule of formamide giving an open-chain compound. The terminal amino group in this compound condensing with the cyano group gives rise to the pyrrole. *p-Methoxyphenylacetonitrile*, reacting with formamide, gives 4-amino-5-(*p*-methoxyphenyl)-pyridine in 23.2% yield. Similar 4-aminopyridines have been obtained from *p*-chloro- and *p*-hydroxyphenylacetonitriles in 51.1% and 24.7% yields. *o*-Methoxy and *p*-nitrophenylacetonitriles give the corresponding 4-aminopyridines in very low yield[303].

Bromo-derivatives of ω-cyanoacetophenone, acetophenone, acetonitrile, phenylacetonitrile and cyanoacetic ester, in which bromine replaces one hydrogen atom in the methyl or methylene group, react with pyridine to form quaternary pyridinium bromides. Thus, with bromoacetonitrile, cyanomethylpyridinium bromide is formed. *Iso*quinoline and quinoline react in a similar manner. Krohnke[194] prepared the following representatives of this class of compounds: ω-cyanophenacylpyridinium bromide, cyanomethylpyridinium bromide, cyanomethyl*iso*quinolinium bromide, cyanobenzylpyridinium bromide, cyanobenzyl*iso*quinolinium bromide, and cyanocarbethoxymethylpyridinium bromide.

According to Hübner, chloral combines with acetonitrile to form the compound[195] $Cl_3CCH(CH_2.CO.NH_2)_2$.

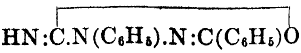
Ethyl *p*-nitrophenylcyanoacetate, $NO_2C_6H_4CH(CN)COOC_2H_5$ is converted to α,β-di-*p*-nitrophenyl-α,β-dicyanoethylsuccinate, $NO_2C_6H_4C(CN)(COOC_2H_5)$.- $C(CN)(COOC_2H_5).C_6H_4NO_2$, m.p. 209°, on oxidation with chromium trioxide; ethyl 2,4-dinitrophenylcyanoacetate is oxidized to ethyl 2,4-dinitrobenzoylformate, $(NO_2)_2C_6H_3.CO.COOC_2H_5$, m.p. 89°[252].

Ethyl bromide reacting with sodio-l-methyl-3-cyano-2-cyclohexanone forms 1-methyl-2-ethoxy-3-cyano-2-cyclohexene; benzyl bromide gives 1-methyl-8-benzyl-3-cyanocyclohexanone. Ethyl bromide gives with sodio-1,3-dimethyl-4-cyano-5-cyclohexanone the compound 1,3-dimethyl-4-cyano-5-ethoxy-4-cyclohexene; allyl bromide gives 1,3-dimethyl-4-allyl-4-cyano-4-cyclohexanone[268].

Potassium cyanoacetate in aqueous solution subjected to the action of a direct electric current between platinum electrodes in the presence of free cyanoacetic acid gives at the cathode principally hydrocyanic acid, formic acid and carbon dioxide. A small amount of succinonitrile also forms according to the equation[253]:

$$2CNCH_2COOH + O \rightarrow CNCH_2CH_2CN + 2CO_2 + H_2O$$

α-Cyanophenylhydrazine, $C_6H_5N(CN).NH_2$, reacting at 70° with benzoyl chloride gives diphenyliminobiazole,



$$HN:\overline{C.N(C_6H_5).N:C(C_6H_5)O}$$ (m.p. 124°)

In acid solution this gives with nitrous acid a nitroso derivative which explodes at 80°, and gives diphenyldiazolone,

$$C_6H_5.N.CO.O.C(C_6H_5):N \text{ (m.p. 113°)}$$

when boiled in acid solution. α-Cyanophenylhydrazine treated with acetyl chloride gives phenyliminoethoxybiazole,

$$HN:C.N(C_6H_5).N:C(OC_2H_5).O \text{ (m.p. 75°)}$$

which in turn gives phenyliminohydroxybiazole,

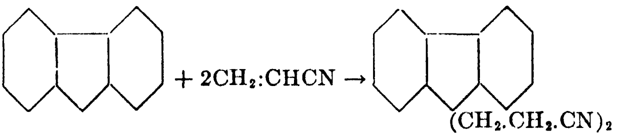
$$HN:C.N(C_6H_5).N:C(OH).O \text{ (m.p. 263°)}$$

when treated with hot sodium hydroxide solution[269].

Sodio diethyl cyanomalonate, $NaC(CN)(COOC_2H_5)_2$, in 1% aqueous solution subjected to the electric current between platinum electrodes at a current density of 0.25 ampere, gives: $(C_2H_5OCO)_2C(CN).C(CN)(COOC_2H_5)_2$, m.p. 56°, in 21% yield[196].

Reactions of Acrylonitrile and Other Unsaturated Nitriles

Reaction with Compounds with Labile or Reactive Hydrogen. Acrylonitrile condenses with a variety of organic compounds having labile hydrogen atoms or active methylenic groups. These reactions occur in the presence of a trace of basic substance such as trimethylbenzylammonium hydroxide (Triton B). The reaction usually takes place at room temperature with evolution of heat. The following is a typical example:

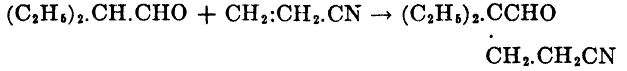


Addition compounds of this type have been obtained from fluorene, indene, anthracene, 2-nitrofluorene, cyclopentadiene, and ω,ω-dimethylbenzofulvene. Acrylic esters do not react in this manner, while crotonic nitrile gives poorly defined, resinous products[197].

Acrylonitrile condenses similarly with reactive ketones having a CH—, CH_2— or CH_3-group adjacent to the carbonyl group, in the presence of strongly basic compounds to form cyanoethyl ketones.

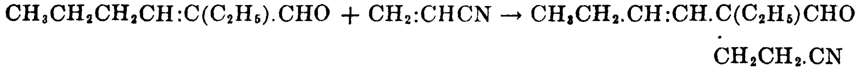
Acetophenone gives a tricyanoethyl compound, $C_6H_5COC(CH_2CH_2CN)_3$. Cyclopentanone, cyclohexanone and *para*-substituted cyclohexanones form tetracyanoethyl derivatives; *o*-methyl cyclohexanone forms a tricyanoethyl compound while α-tetralone gives a dicyanoethyl derivative. Acetone gives a tricyanoethylated product, $CH_3COC(CH_2.CH_2CN)_3$. Ketones of the type, $R.CH_2.CO.CH_3$, first yield a disubstituted compound, $R.C(CH_2CH_2CN)_2.CO.CH_3$, and on further reaction, more highly substituted products. Acetoacetic esters react to form dicyanoacetylated compounds[198]. *p*-Bromoacetophenone yields a tricyanoethyl derivative, $BrC_6H_4CO.$-$C(CH_2CH_2CN)_3$[328]. Cyclohexanone gives a 2,2,6,6-tetracyanoethyl derivative[329].

Aldehydes of the type, R_1R_2CHCHO, such as diethyl acetaldehyde, bearing an α-hydrogen, react with acrylonitrile in the presence of a base forming the α-cyanoethylated aldehyde:



$$(C_2H_5)_2.CH.CHO + CH_2{:}CH_2.CN \rightarrow (C_2H_5)_2.\underset{\displaystyle \cdot\; CH_2.CH_2CN}{C}CHO$$

α,β-Unsaturated aldehydes of the type of α-ethyl-β-propylacrolein undergo a 1,3-hydrogen shift and likewise yield α-cyanoethylated derivatives:



$$CH_3CH_2CH_2CH{:}C(C_2H_5).CHO + CH_2{:}CHCN \rightarrow CH_3CH_2.CH{:}CH.\underset{\displaystyle \cdot\; CH_2CH_2.CN}{C}(C_2H_5)CHO$$

The reaction takes place particularly well in the presence of a 50% aqueous solution of potassium hydroxide.

The aldehydonitriles obtained may be converted to the corresponding acids by hydrolysis. The sodium salt of these acids yield, upon reduction, the sodium salt of the corresponding δ-hydroxy acid. On acidification of the sodium salt, the corresponding δ-lactone forms[199].

Certain α,β-unsaturated compounds, such as mesityl oxide, crotononitrile, crotonamide and γ-ethyl-β-propylacrolein undergo a shift in a hydrogen atom and react with acrylonitrile to give β-cyanoethylated products.

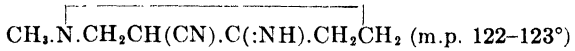
Nitro compounds of the type RCH_2NO_2 or $RR'CHNO_2$, which contain a reactive hydrogen adjacent to the nitro group, react with acrylonitrile in the presence of alkaline agents to form mono- or di-β-cyanoethyl nitro compounds of the type $RCH(NO_2)CH_2CH_2CN$ or $RC(NO_2)(CH_2CH_2CN)_2$. The reaction is best carried out in the temperature range 30° to 60°[304].

Sodio diethyl malonate reacts with acrylonitrile in alcoholic solution at 65° to form ethyl α-carbethoxy-γ-cyanobutyrate in 40 to 45% yield; reduced in the presence of Raney nickel under 2000 lb hydrogen pressure this gives ethyl 2-ketonipecotate in 57% yield. Ethyl γ-carbethoxy-α-cyanobutyrate is obtained through the interaction of sodio ethyl cyanoacetate and ethyl acrylate in alcoholic solution; ethyl 5-ketonipecotate is obtained when this compound is reduced catalytically[279].

Acrylonitrile reacts with amines, forming β-amino propionitriles[200], $RNH.$-$CH_2.CH_2.CN$. Both primary and secondary amines may form simultaneously. Seven molecular equivalents of ammonia reacting with acrylonitrile at 40° yield 22% primary and 64% secondary aminopropionitrile. Piperidine is the most reactive among amines, morpholine ranking next. Diethylamine is the most reactive among aliphatic nitriles; reactivity of other aliphatic amines decreases in general with increasing molecular weight. Aromatic amines and certain heterocyclic amines react only in the presence of a catalyst. Aniline reacts at 180° in the presence of copper sulfate; carbazole reacts vigorously in the presence of benzyltrimethylammonium hydroxide; tetrahydroquinoline reacts well in acetic acid solution. Anisidine, 2-aminopyridine and urea do not react[254]. Burckhalter and co-workers[201] have prepared β-di(β′-ethylhexyl)-aminopropionitrile, b.p.$_2$ 163–

164° and β-di-*n*-octylaminopropionitrile. Isatin reacting with acrylonitrile in the presence of trimethylbenzyl ammonium hydroxide gives 1-(2-cyanoethyl)isatin[305].

Cook and Reed obtained β-cyanoethylmethylamine, $CH_3NHCH_2CH_2CN$, in 78% yield through the interaction of methylamine and acrylonitrile in methanol solution at ordinary temperature for 24 hours. The tertiary compound $CH_3N(CH_2CH_2CN)_2$ was obtained upon heating a mixture of acrylonitrile and methyl amine in a sealed tube at 80° for 16 hours. The tertiary compound was converted to 4-imino-3-cyano-1-methylpyridine,



$$CH_3.N.CH_2CH(CN).C(:NH).CH_2CH_2 \text{ (m.p. 122–123°)}$$

by treatment with metallic sodium in toluene[306].

An elegant method for the preparation of alanine, developed by Galat, is based upon the reaction of phthalimide with acrylonitrile. The reaction proceeds quantitatively upon boiling the mixture of the reagents in the presence of trimethylbenzyl ammonium hydroxide for twenty minutes:

$$C_6H_4(CO)_2NH + CH_2{=}CHCN \rightarrow C_6H_4(CO)_2N.CH_2.CH_2CN$$

Alanine is obtained in 80% yield from the compound by boiling it under reflux with 20% hydrochloric acid for four hours[307].

Ammonia reacts with vinylacetonitrile, slowly in the cold, more rapidly when heated in a sealed tube at 75°, forming β-aminobutyronitrile in small yield; a small quantity of the secondary aminonitrile $CN.CH_2.CH(CH_3).NH.CH(CH_3)CH_2.CN$, and isomeric crotonic nitriles also are produced. Methylamine gives β-methylaminopropionitrile; dimethylamine reacts rapidly forming β-dimethylaminopropionitrile; ethylamine in 33% aqueous solution reacts almost instantaneously with evolution of heat forming β-ethylaminobutyronitrile, b.p. 192–193° (dec.), in 80% yield. Some of the higher aliphatic amines such as diethylamine, isobutylamine, ethylenediamine transform vinylacetonitrile to a mixture of isomeric crotonic nitriles. Trimethylammonium hydroxide first gives an addition product $CN.CH_2.CH[N(CH_3)_3.OH].CH_3$ which is unstable and changes to β-dimethylaminobutyronitrile. Piperidine gives with vinylacetonitrile, β-piperidinobutyronitrile[255]. Aromatic amines react only in the presence of a catalyst (cuprous chloride). β-Anilino-, β-*o*-, *m*- and *p*-toluidinobutyronitriles have been prepared[256]. Diphenylamine does not react but causes the isomerization of the nitrile.

Acrylonitrile, treated with water at moderately high temperatures in the presence of alkalies, gives β,β′-dicyanoethyl ether, $CNCH_2CH_2OCH_2CH_2CN$[308].

Alcohols, reacting with acrylonitrile or other α,β-unsaturated nitriles in the presence of an alkali metal, alkali metal hydroxide or a tertiary amine, yield β-alcoxypropionitriles.

As an example of the procedure, 0.5 gm of sodium is dissolved in 29 gm of absolute alcohol and 53 gm of acrylonitrile are added to the solution under cooling and agitation. The mixture is allowed to stand for two hours, then 1 gram of dry hydrogen chloride is added and the product is isolated by fractional distillation. Approximately 94 gm of β-ethoxypropionitrile boiling between 167° and 173° are thus obtained[309].

Primary and secondary alcohols react readily; tertiary alcohols such as *tert*-butyl alcohol react poorly unless the hydroxyl group is activated through the presence, for example, of an acetylenic group as in $(CH_3)_2C(OH)C{\equiv}CH$. Phenols also react in the same manner as alcohols. Hydroxy cyano- and hydroxy carboxylic compounds have been condensed with α,β-unsaturated nitriles. Diamino compounds have been prepared by reducing the condensation product with the former[310].

Substituted ethanolamines, $R_2NCH_2CH_2OH$, have been condensed with acrylonitrile in the presence of sodium ethoxide to $R_2NCH_2CH_2OCH_2CH_2CN$[264]. Compounds of the type $HOCH_2C(R)_2.NH_2$, condensed with acrylonitrile, yield β-(hydroxyamino)-propionitriles, $HOCH_2C(R)_2NHCH_2CH_2CN$. These nitriles have been reduced to primary amines by hydrogenation in the presence of ammonia, by use of Raney nickel as a catalyst[311]. Acrylonitrile has been condensed with di- and polyhydroxy derivatives to di- and poly-β-cyanoethyl ethers[312]. Bis-(β-cyanoethyl)-diethyleneglycol ether, $(CNCH_2CH_2OCH_2CH_2)_2O$ has been obtained through the condensation of acrylonitrile with diethylene glycol[313].

β-Diethylaminoethylmercaptan, $(C_2H_5)_2NCH_2CH_2SH$, has been condensed with acrylonitrile to β-diethylaminoethyl-β'-cyanoethyl sulfide, $(C_2H_5)_2N.CH_2CH_2SCH_2CH_2CN$, in 92% yield[314]. Thiazyl sulfides reacting in the presence of sodium hydroxide or other catalyst give cyanoethylthiazyl sulfides, $RS.CH_2CH_2CN$[271].

Nitrogen ring compounds in which a hydrogen atom is attached to nitrogen also react with acrylonitrile in the presence of catalysts such as copper salts, phenols, hydroquinone, resorcinol, to form the N-β-cyano ethyl derivative of the cyclic amine[315].

Benzenediazonium chloride, $C_6H_5N_2Cl$, reacts with acrylonitrile to form α-chloro-β-phenylpropionitrile[265], $C_6H_5CH_2.CHCl.CN$.

Acrylonitrile reacts in aqueous solution and in the cold with the alkali compound of cellulose to form a cyanoethylcellulose, as many as three moles of acrylonitrile reacting per glucose unit of cellulose. In these compounds the cyanoethyl group replaces the hydrogen in hydroxy groups in cellulose[266].

Paraformaldehyde, reacting with methallyl cyanide, $CH_2{:}C(CH_3)CH_2CN$, in 50% sulfuric acid at 50°, gives methylcyano-*m*-dioxane[316],

$$\overline{CH_2CH(CH_3).CH(CN)O.CH_2.O}$$

Diazomethane reacting with methylacrylonitrile, $CH_2{:}C(CH_3)CN$, gives an addition product, probably methyl-5-cyano-5-Δ^1-pyrazoline, which on heating is transformed to 1-methylcyclopropylcyanide

$$\overline{CH_2CH_2C}(CH_3).CN \quad (\text{b.p.}_{761.5} = 127\text{–}127.5^\circ)$$

This compound has been hydrolyzed to tiglic acid by the use of phosphoric acid[267].

Lactonitrile reacting with acrylonitrile in the presence of an alkaline catalyst at 90° gives α,β-dicyanodiethyl ether[278], $CNCH_2CH_2OCH(CN)CH_3$.

Acrylonitrile reacts with chloroform in the presence of alkaline catalysts to form γ-trichlorobutyronitrile, $Cl_3CCH_2.CH_2CN$, m.p. 41°, b.p. 214–216°.

The reaction may be carried out by mixing chloroform cooled to 2° with 1/10 its weight of 40% aqueous trimethylbenzylammonium chloride also cooled to 2° and slowly adding a molecular equivalent of acrylonitrile under agitation and cooling. The mixture is then held at 0–5° and continually agitated for 24 hours, a little more of the aqueous solution of the base chloride (1/4 of the original) being added at the end of eight hours. The halobutyronitrile is isolated by distillation from the washed reaction product.

The corresponding bromo compound may be prepared in a similar manner from bromoform[317].

Treated in an aqueous medium with gaseous chlorine at 20–30°, acrylonitrile is converted largely to α,β-dichloropropionitrile, a certain amount of α-chloro-β-hydroxypropionitrile also resulting[318].

When chlorine is passed directly into acrylonitrile maintained at 10–60° trichloropropionitrile results. The latter is also obtained through the direct chlorination of α,β-dichloropropionitrile. The product may be isolated by distilling under 60–90 mm pressure[319].

α-Chloroacrylonitrile results when vapors of acrylonitrile mixed with chlorine are passed over active carbon heated to 200–500°[320]. α-Chloroacrylonitrile is also obtained through the removal of one chlorine atom from α,β-dichloroacrylonitrile with the required quantity of a base[321]. Dihaloacrylonitriles are obtained by treating trihalopropionitrile with a tertiary amine such as quinoline boiling above 200°, the dihaloacrylonitrile being removed from the reaction zone, by distillation, as it is formed[322].

On treating acrylonitrile and other α,β-unsaturated nitriles with hypochlorous acid, or with chlorine in aqueous solution at 16 to 20°, α-chloro-β-hydroxynitriles such as $HOCH_2CH(Cl).CN$ are obtained.[330]

Acrylonitrile, hydrogenated in solution under 6 atm. pressure between 20 and 75° in the presence of Raney nickel, is converted to propionitrile[323].

Under suitable conditions acrylonitrile and butadiene may be made to combine to give rubber-like or resinous co-polymeres. The rubbery polymers, which may be vulcanized like natural rubber, have outstanding oil resistant qualities and exhibit great resistance to abrasion. These polymers have assumed considerable importance in the field of *synthetic rubbers.*

Polymerization is carried out at about 50° in an aqueous medium in which the mixture of the two liquids is dispersed in the form of an emulsion. Sodium oleate, sodium stearate or the sodium salt of acid sulfuric esters of high molecular weight alcohols are used as emulsifying agents. Polymerization is brought about with the aid of catalysts such as sodium perborate, hydrogen peroxide or an organic peroxide. Carbon tetrachloride, chlorobenzene, ethylene dichloride, and other similar compounds are used as activators or promoters. The properties of the final polymer may be varied within limits by varying the proportions of acrylonitrile and butadiene. Perbunan, Hycar, Chemigum and Butaprene are acrylonitrile-butadiene co-polymers.

Diene Condensation. Cyclic nitriles, such as Δ^1-tetrahydrobenzonitrile, have been obtained through the interaction, in aqueous dispersion, of 1,3-butadiene and acrylonitrile or substituted acrylonitriles in the presence of copper and manganese or their salts[324]. A condensation product has also been obtained with fulvene[197]. The reaction of acrylonitrile with alloöcymene and with mycene in the presence of 1% hydroquinone led to the formation of 2-(3-*iso*hexenyl)-5-cyanocyclohexene and 3-(1-methylpropenyl)-4-cyano-6,6-dimethylcyclohexene respectively[325]. Fumaronitrile, CNCN=CHCN, has been condensed with cyclopentadiene to *trans*-1,2,3,6-tetrahydro-3,6-methanophthalonitrile in 90% yield; with diphenylfulvene to trans-1,2,3,6-tetrahydro-3,6-benzohydrylidenemethanophthalonitrile in 25% yield. The corresponding condensation products with maleonitrile and dicyanoacetylene have also been prepared[326].

Reactions of Acetylenic Nitriles

Acetylenic nitriles, RC≡C.CN, condense readily in the cold with sodium alcoholates, R'ONa, forming sodio compounds, RC(OR'):CNa.CN, which on hydrolysis yield RC(OR'):CH.CN. Disubstituted compounds, $RC(OR')^2.CH_2CH$, are also formed simultaneously, and the separation of the two compounds is difficult because of the proximity of their boiling points. Condensation products[202] have been prepared from amyl-, hexyl- and phenyl-propiolic nitriles and CH_3ONa, C_2H_5ONa and $CH_3CH_2CH_2ONa$.

Sodium salts of phenolic compounds, R''ONa, also condense with acetylenic nitriles forming the compounds, RC(OR''):CNaCN, which on hydrolysis give: RC(OR''):CH.CN.

Moureu and Lazennec[203] prepared these compounds in the following manner:

One equivalent of metallic sodium was dissolved in a large excess of molten phenol by the application of heat; the solution was warmed to 120° and one molecular equivalent of nitrile was added under good agitation. The temperature was then raised and maintained at 140° for a few hours while the mixture was agitated. After the completion of the reaction, the excess phenol was distilled off, and the residue was extracted with boiling benzene, the solution was washed with aqueous alkali to eliminate the remaining free phenol and was finally evaporated to dryness. The product was purified by repeated crystallization.

The following compounds were prepared[203]:

	Melting Point °C	*Boiling Point °C*	*Under mm Hg*	*Density*	*At °C*
$C_5H_{11}C(OC_6H_5)$:CH.CN	....	175–178	15	0.9841	20
$C_6H_{13}C[OC_6H_4CH_3(o)]$:CH.CN	....	195–196	15	0.9707	20
$C_6H_5C(OC_6H_5)$:CH.CN	85–86				
$C_6H_5C[OC_6H_4CH_3(o)]$:CH.CN	104–105				
$C_6H_5C[OC_6H_3(CH_3)(C_3H_7)\text{-}3{:}6]$:HC.CN	....	226–229	11	1.054	23
$C_6H_5C[OC_6H_4OCH_3(o)]$:CH.CN	90–91				

Amines react with acetylenic nitriles to form β-aminoacrylonitriles:

$$R.C\equiv CCN + HNR'R'' \rightarrow R.C(NR'R''):CH.CN$$

Moureu and Lazennec[204] prepared the following by this reaction:

	Melting Point °C	*Boiling Point °C*	*Under mm Hg*
$C_6H_5C(NC_5H_{10}):CH.CN$	....	218–220	13
$C_6H_5C(NH.CH_2C_6H_5):CHCN$			
$C_6H_5C(NHC_2H_5):CHCN$	135–136		
$C_6H_5C[N(C_2H_5)_2]:CHCN$	70		
$C_5H_{11}.C(NHCH_2C_6H_5):CH.CN$	64.5		
$C_5H_{11}.C(NC_5H_{10}):CH.CN$	....	205–206	18
$C_6H_{13}.C(NHCH_2C_6H_5):CH.CN$	48		
$C_6H_{13}.C(NC_5H_{10}):CHCN$	....	235–238	17

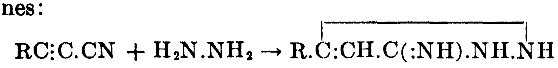
These amino-compounds are readily hydrolyzed to ketonitriles:

$$C_5H_{11}C(NC_5H_{10}):CH.CN + H_2O \rightarrow C_5H_{11}.CO.CH_2CN + NHC_5H_{10}$$

Hydrolysis is carried out as follows:

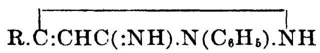
One molecular equivalent of the aminonitrile is dissolved in eight times its volume of a mixture of 25% alcohol (95%) and 75% ether containing 11.5 gm oxalic acid in solution per 100 cc. The solution is allowed to stand a few hours and the precipitate which forms is filtered. The filtrate is evaporated to ¼ its original volume, washed with water, dried over anhydrous sodium carbonate and finally the remaining ether is evaporated off. The yeild is nearly quantitative[205].

Acetylenic nitriles condense with *hydrazine hydrate* in the cold forming pyrazoloneimines:



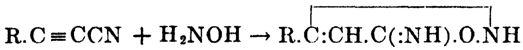
$$RC{:}C.CN + H_2N.NH_2 \rightarrow R.\overline{C{:}CH.C({:}NH).NH.N}H$$

Phenylhydrazine gives phenylpyrazoleneimines[206]:



$$R.\overline{C{:}CHC({:}NH).N(C_6H_5).N}H$$

Acetylenic nitriles condense similarly with *hydroxylamine* in cold alcoholic solution, forming *iso*xazoloneimines:



$$R.C{\equiv}CCN + H_2NOH \rightarrow R.\overline{C{:}CH.C({:}NH).O.N}H$$

3-Phenyl-, 3-amyl- and 3-hexyl-5-*iso*xazoloneimines have been prepared by this reaction[207].

Condensation Reactions with Dimeric Nitriles

Acid chlorides react with dinitriles in the presence of pyridine, forming acylated derivatives. By this reaction, Benary and Rosenfeld prepared α-phenoxy acetylated diacetonitrile, benzoacetodinitrile and *p*-toluacetodinitrile; α-cinnamoylated diacetonitrile and benzoacetodinitrile[208].

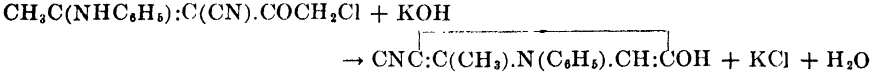
Diacetonitrile readily forms a chloroacetyl compound with *chloroacetyl chloride* in ether solution and in the presence of pyridine:

$$CH_3C(NH_2):CHCN + ClCO.CH_2Cl \rightarrow CH_3C(NH_2):C(CN).COCH_2Cl + HCl$$

Benzoacetodinitrile and other arylacetodinitriles react in the same way. From these compounds, β-thio-bis-acetyldiacetonitriles have been obtained:

$$2CH_3C(NH_2){:}C(CN).CO.CH_2Cl + KHS \rightarrow [CH_3C(NH_2){:}C(CN)COCH_2]_2S + KCl + HCl$$

Alcoholic potassium hydroxide condenses the chloracetyl derivatives to pyrroles[209]:



$$CH_3C(NHC_6H_5){:}C(CN).COCH_2Cl + KOH \rightarrow CNC{:}C(CH_3).N(C_6H_5).CH{:}COH + KCl + H_2O$$

Condensation takes place also in the presence of ammonia. By this reaction, anhydro-2,3′-bis-(3-keto-5-*p*-tolylpyrrolin-4-nitrile) and anhydro-2,3′-bis-(3-keto-5-*p*-methoxyphenylpyrrolin-4-nitrile) have been made from C-chloracetylated *p*-toluacetodinitrile and C-chloroacetyl-*p*-anisylacetodinitrile, respectively[210].

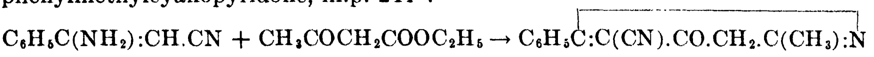
Oxalic ester chloride, $C_2H_5OCO.COCl$, gives C-ethoxalyl-*p*-toluacetodinitrile, $CH_3.C_6H_4C({:}NH).CH(CN).CO.COOC_2H_5$, with *p*-toluacetodnitrile. *Oxalyl chloride* gives C-oxalyl-bis-diacetonitrile with diacetonitrile[211].

Diacetonitrile condenses with *diethyl oxalate* in the presence of sodium ethoxide to the N-acylated derivative:

$$CH_3C(NH_2){:}CH.CN + C_2H_5OCO.COOC_2H_5 \rightarrow CH_3C(NHCO.COOC_2H_5){:}CHCN + HOC_2H_5$$

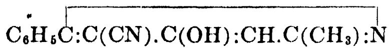
This reaction takes place also with other esters. N-phenoxyacetyldiacetonitrile benzoacetodinitrile[212]; toluacetodinitrile, N-cinnamoyldiacetonitrile and benzo acetodinitrile[213] have been made. Meyer[212], who prepared a number of condensation products of dinitriles with esters, wrongly regarded the compounds as C-acylated derivatives.

Dinitriles react with *β-ketoesters* in the presence of hydrogen chloride, forming cyanopyridine derivatives. Thus, benzoacetodinitrile gives with *ethyl acetoacetate* phenylmethylcyanopyridone, m.p. 244°:



$$C_6H_5C(NH_2){:}CH.CN + CH_3COCH_2COOC_2H_5 \rightarrow C_6H_5C{:}C(CN).CO.CH_2.C(CH_3){:}N$$

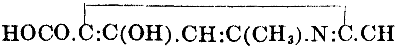
or



$$C_6H_5C{:}C(CN).C(OH){:}CH.C(CH_3){:}N$$

This compound, heated at 200° with concentrated hydrochloric acid, gives phenylmethyl-γ-hydroxypyridine, colorless needles, melting at 178.5°.

Diacetonitrile heated to boiling with ethyl acetoacetate in the presence of a little pyridine gives γ-hydroxy-α, α′-lutidine-β-carboxylic acid[257],



$$HOCO.C{:}C(OH).CH{:}C(CH_3).N{:}C.CH_3$$

Benzoacetodinitrile reacts with amyl nitrite forming the compounds $C_6H_5C({:}N.NO).C(CN){:}NOH.NH_3$, m.p. 152–152.5°, and $C_6H_5CO.C(CN){:}NOH$, m.p. 120–121°. From *p*-toluacetodinitrile, a product melting at 156° is obtained, while diacetonitrile forms a compound melting at 122°[214].

Cyanoacetic acid, reacting with acetodinitrile in the absence of water at 140°, gives 2,4-dimethyl-3-cyano-6-aminopyridine, m.p. 222° and a compound of unknown structure, $C_{12}H_{10}N_2O$, melting with decomposition above 220°. In the presence of water, 2,4-dimethyl-3-cyano-6-hydroxypyridine forms. This is also the main product of the reaction between succinic- and α-hydroxy acids in alcoholic solution with acetodinitrile. *p*-Toluacetodinitrile gives with succinic acid 2,4-di-*p*-tolyl-3-cyano-6-hydroxypyridine, m.p. 265°; benzoacetodinitrile does not form a definite compound. In alcoholic solution at 80°, benzoacetodinitrile is transformed by *glycolic acid* to 2,4-diphenyl-3-cyano-6-ethoxypyridine, needles, melting at 141–142°. *α-Hydroxyisobutyric acid*, heated with benzoacetodinitrile at 150°, gives 2,4-diphenyl-3-cyano-6-hydroxypyridine, needles, melting at 192°; heated at 140° with *malic acid*, the same dinitrile gives 2,4-diphenyl-3-cyano-6-ethoxypyridine.

Dinitriles form pyrrolones with *phenyl-α-hydroxyacetic* and *lactic acids*[215]. Thus, benzoacetodinitrile heated with lactic acid in alcoholic solution in a sealed tube at 150° gives 2-methyl-5-phenyl-Δ^4-pyrrolone-3-carboxylic acid[158]

$$HOCO.C{:}C(C_6H_5).NH.C(CH_3){:}COH$$

Similarly *p*-toluacetodinitrile, heated with phenyl-α-hydroxyacetic acid in alcoholic solution at 150°, forms 3-phenyl-5-*p*-tolyl-4-cyano-2-pyrrolone:

$$CH_3C_6H_4C(NH_2){:}CH.CN + C_6H_5CH(OH).COOH$$
$$\rightarrow CH_3C_6H_4C{:}C(CN).CH(C_6H_5).CO.NH + 2H_2O$$

The compound crystallizes in needles melting at 220°; it is insoluble in water, slightly soluble in ether. Under the same conditions, benzoacetodinitrile gives 2,5-diphenyl-4-cyano-3-pyrrolone, colorless needles, melting at about 230°, soluble in ether and chloroform. This dinitrile gives with lactic acid 2-methyl-5-phenyl-4-cyano-3-pyrrolone, needles, melting with decomposition at 170°. Attempts to cause benzoacetodinitrile to react with oxalic acid have failed.

Dinitriles condense with *aldehydes* and *ketones*, forming 3,5-dicyano-1,4-dihydropyridines:

$$2RC(NH_2){:}CH.CN + OC(R')R''$$
$$\rightarrow CN.C{:}C(R).NH.C(R){:}C(CN).C(R')R'' + H_2O + NH_3$$

These compounds are converted on oxidation with nitrous acid to derivatives of 3,5-dicyanopyridine[217].

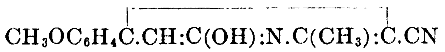
The yields of dihydropyridines obtained by Meyer[216] from acetodinitrile and various ketones were as follows:

Ketone	*Yield of Corresponding Dihydropyridine, %*
CH_3COCH_3	67
$CH_3COC_2H_5$	62
$CH_3COC_3H_7$	58.5
$CH_3.CO.CH_2C_6H_5$	52.5
$C_2H_5CO.C_2H_5$	34
$CH_2(CH_2)_4.CO$	75
$C_6H_9(CH_3)O$ (methylcyclohexanone)	69

Meyer[216] also prepared dihydropyridines with *benzoacetodinitrile* and ketones in yields varying between 23.2 and 87% and from *p*-toluacetodinitrile and ketones, the yields in this case ranging between 71 and 88.5% The cyano group in these compounds resists hydrolysis. This type of condensation products have also been obtained through the condensation of *p*-ethoxybenzoacetodinitrile, $C_2H_5OC_6H_4C(:NH)CH_2CN$, with ethyl methyl ketone and benzaldehyde[259].

m- and *p*-Hydroxybenzaldehydes react normally; salicylaldehyde reacts normally with p-tolylacetodinitrile; with other dinitriles two molecules of the aldehyde condense with one of nitrile and elimination of two molecules of water[260]. Palit[261] prepared the condensation products of these aldehydes with benzoacetodinitrile, *p*-tolylacetodinitrile and anisylacetodinitrile.

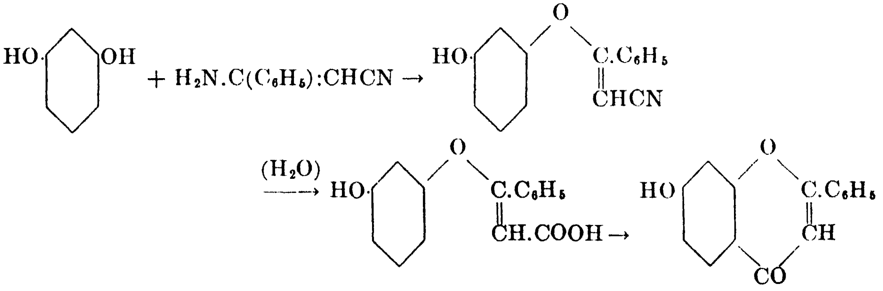
Anisalacetophenone, $CH_3OC_6H_4CH:CH.CO.C_6H_5$, reacts with diacetonitrile in alcoholic solution in the presence of sodium ethoxide forming 2-methyl-6-phenyl-4-(4-methoxyphenyl)-nicotinonitrile[262],



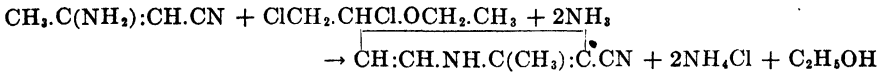
$$CH_3OC_6H_4C.CH:C(OH):N.C(CH_3):C.CN$$

Similar compounds are obtained through the interaction of anisalacetophenone and benzoacetodinitrile[263] and *p*-toluacetodinitrile[262].

Benzoacetodinitrile condenses with *resorcinol* in presence of hydrogen chloride to 3-hydroxyflavone[218]:

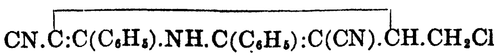


Diacetonitrile reacts with *α,β-dichlorodiethyl* ether in aqueous ammonia to form 2-methyl-3-cyanopyrrole in about 20% yield:



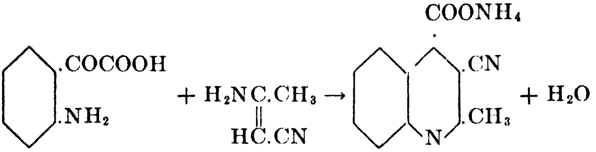
$$CH_3.C(NH_2):CH.CN + ClCH_2.CHCl.OCH_2.CH_3 + 2NH_3$$
$$\rightarrow CH:CH.NH.C(CH_3):C.CN + 2NH_4Cl + C_2H_5OH$$

The cyano group in this compound is quite inactive; it does not undergo the Stephen reaction, is not hydrolyzed to a carboxyl group and cannot be reduced either catalytically or with sodium and alcohol[219,220]. Benzoacetodinitrile reacts with α,β-dichlorodiethyl ether forming 4′-chloro-2,6-diphenyldihydro-γ-picoline-3,5-dinitrile[220],



$$CN.C:C(C_6H_5).NH.C(C_6H_5):C(CN).CH.CH_2Cl$$

Isatic acid condenses with acetodinitrile forming a salt of 2-methyl-3-cyanoquinoline-4-carboxylic acid:

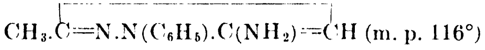


Benzo- and *p*-toluacetodinitriles similarly give salts of 2-phenyl-3-cyanoquinoline carboxylic acid (m.p. of acid 267–268°) and 2-*p*-tolyl-3-cyanoquinoline carboxylic acid (m.p. of acid 215°) respectively in low yield.

o-Aminoacetophenone, heated in a sealed tube at 150° with a solution of acetodinitrile in acetic acid, gives 2,4-dimethyl-3-cyanoquinoline, needles, melting at 161–162°. With benzoacetodinitrile there is obtained 2-phenyl-4-methyl-3-cyanoquinoline, needles, melting at 166–167°; with *p*-toluacetodinitrile, 2-*p*-tolyl-4-methyl-3-cyanoquinoline, yellow needles, melting at 140°.

α-Aminobenzaldehyde reacts directly with acetodinitrile forming 2-methyl-3-cyanoquinoline, needles or prisms melting at 131°. Condensation takes place with benzoacetodinitrile at 180° while *p*-toluacetodinitrile does not react[215,221].

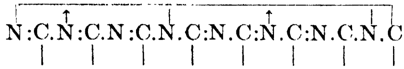
Acetodinitrile reacting with phenylhydrazine gives 1-*phenyl*-3-*methyl*-5-*aminopyrazole*[294],



$CH_3.C{=}N.N(C_6H_5).C(NH_2){=}CH$ (m. p. 116°)

Phthalocyanines

Phthalonitrile may be condensed under the proper conditions to a complex consisting of four molecules of the nitrile joined by nitrogen bonds:*



$N{:}C.N{:}C.N{:}C.N.C{:}N.C{:}N.C{:}N.C.N.C$

Alternate carbon atoms are joined to two neighboring carbon atoms of a phenyl group; and, in metal phthalocyanine, the fourth and last nitrogen atoms are attached to a divalent metal with principal valencies, indicated by dashes; the second and sixth nitrogen atoms are attached to the metal atom by coordinate valencies indicated by arrows. The atomic grouping in phthalocyanine is similar to that in porphin; phthalocyanine may indeed be considered tetrabenzotetrazoporphin. Condensation takes place exothermally on heating phthalonitrile with various metals such as copper or a copper salt. For ease of control, the reaction is carried out in an inert solvent.

Cuprous chloride reacts with phthalonitrile at 170° to form copper phthalocyanine. Cupric chloride gives a chlorinated compound $(C_8H_4N_2)_3Cu.C_8H_3Cl.N_2$. Litharge heated with phthalonitrile gives lead phthalocyanine in good yield. Aluminum chloride reacts with phthalocyanine in boiling quinoline to form chloroaluminum phthalocyanine, $C_{32}H_{16}N_8.AlCl$, and a chlorinated product, $(C_8H_4N_2)_3$.-

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* H. de Diesbach and van der Weid were the first to prepare a phthalocyanine (*Helv. Chim. Acta.*, **10**, 886 (1927)). They obtained it by the interaction of *o*-dibromobenzene and cuprous cyanide in pyridine solution. These workers noted the deep blue color and the great stability of the material, but failed to appreciate its commercial value.

$C_8H_3Cl.N_2.AlCl$. Tin gives phthalocyanine tin dichloride, $(C_{32}H_{16}N_8)SnCl_2$, which may be reduced to tin phthalocyanine, $(C_{32}H_{16}N_8)Sn$. A tin diphthalocyanine, $(C_{32}H_{16}N_8)_2Sn$, has also been obtained through the interaction of the dichloro-compound with sodium phthalocyanine.

In addition to the above, the phthalocyanines of the following metals have been prepared: lithium, sodium, potassium, silver, beryllium, magnesium, calcium, zinc, barium, cadmium, mercury, vanadium, antimony, molybdenum, manganese, iron, cobalt, nickel, palladium and platinum.

Copper and platinum form stable coördination compounds that are soluble in high boiling organic solvents and may be sublimed at 500–600°. They are stable toward cold concentrated sulfuric acid and hot alkalies, and the metal cannot be removed from these without causing the decomposition of the phthalocyanine group.

Copper phthalocyanine, as obtained by the reaction of cuprous chloride with phthalonitrile, is a bright blue, insoluble mass which has little or no value as a pigment. It is conditioned by dissolving in concentrated sulfuric acid and running the solution into a large volume of water and finally hydrolyzing the sulfate to free copper phthalocyanine. The precipitate, obtained as a paste, is further dispersed, mixed with water soluble diluents and dried.

The phthalocyanine pigments are all of blue or green color. They are insoluble in water and insoluble or only slightly soluble in organic solvents. They dissolve in concentrated sulfuric, phosphoric and chlorsulfonic acids, anhydrous hydrogen fluoride, ethyl sulfuric and trichloracetic acids. They are heat-resistant, and may be sublimed at about 500°.

Free *phthalocyanine* may be prepared in about 15% yield by heating phthalonitrile and sodamide in quinoline. Metal-free phthalocyanine may also be prepared from certain metallic phthalocyanines by the removal of the metal. Thus, magnesium phthalocyanine treated with an acid gives free phthalocyanine in 40% yield. Other phthalocyanines, from which the metal may be readily removed, are sodium-, calcium-, mercury-, tin and manganese phthalocyanines. The removal of the phthalocyanine may often be effected by heating the metallic compound in a high boiling organic solvent.

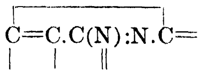
The reactivity of the aromatic nuclei in phthalocyanines is of a rather low order. Attempts to introduce alkyl or acyl groups by the Friedel-Crafts reaction have not been successful. Attempts to nitrate the nuclei have been equally unsuccessful. These compounds may be chlorinated in an anhydrous medium at a relatively high temperature. A maximum of sixteen chlorine atoms may be introduced into the molecule. Phthalocyanines can be readily oxidized in an acid medium. The reaction with ceric sulfate proceeds quantitatively and may be utilized for the quantitative determination of phthalocyanine:

$$(C_8H_4N_2)_4Cu + 3H_2SO_4 + 7H_2O + O \rightarrow 4C_8H_5O_2N + CuSO_4 + 2(NH_4)_2SO_4$$

Phthalocyanine-like condensation products with metals may be obtained from compounds containing nitrile groups attached to adjacent carbon atoms. The conditions that must be satisfied are the following:

There must be present a double bond between the carbon atoms to which the nitrile groups are attached. The double bond may form during the reaction leading to the formation of the complex.

The compound should be capable of forming a ring system:



$$\mathrm{C{=}C.C(N){:}N.C{=}}$$

The nitrile should be resistant to heat up to the temperature at which the transformation into the complex takes place.

Centers of reactivity capable of combination with the metal or of destroying the ketyl-groups which form as intermediates should be absent.

Phthalocyanine-like complexes have been prepared from thiophene-2,3-, thionaphthene-2,3-, pyridine-2,3- and pyrazine-2,3-dinitriles.

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Chapter 16

Knoevenagel Condensation

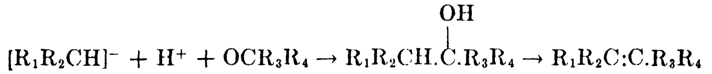
Aldehydes and ketones, in general, condense with nitriles containing an active methylenic group according to the equation:

$$R_1R_2CH_2 + OCR_3R \rightarrow R_1R_2C{:}CR_3R_4$$

This reaction, which is quite general, was extensively studied by Knoevenagel and will be referred to as the Knoevenagel condensation.

Hann and Lapworth[1] consider the mechanism of the reaction as follows:

$$R_1R_2CH_2 \rightleftarrows [R_1R_2CH]^- + H^+$$



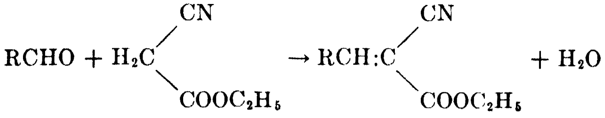
$$[R_1R_2CH]^- + H^+ + OCR_3R_4 \rightarrow R_1R_2CH.\overset{OH}{\overset{|}{C}}.R_3R_4 \rightarrow R_1R_2C{:}C.R_3R_4$$

Amines and sodium alcoholate act as catalysts for the reaction. Cope[2] showed that ammonium- and amine acetates are more effective catalysts than free ammonia and amines, and that the weekly basic compound acetamide is an effective catalyst when used in acetic acid solution. The reaction is reversible.

The condensation of aldehydes with cyanoacetic acid and its esters proceeds well in aqueous solution in the presence of potassium bromoacetate and potassium cyanide[85].

Condensations with Cyanoacetic Ester

Cyanoacetic esters may be condensed with aldehydes according to the Knoevenagel reaction to form unsaturated nitriles[3]:

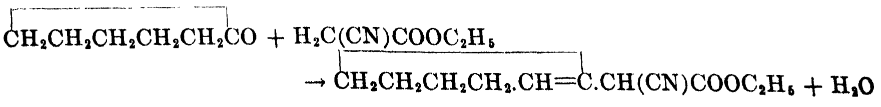


$$RCHO + H_2C\begin{matrix}\diagup CN \\ \diagdown COOC_2H_5\end{matrix} \rightarrow RCH{:}C\begin{matrix}\diagup CN \\ \diagdown COOC_2H_5\end{matrix} + H_2O$$

Ketones also react normally in a similar manner[2]:

$$R_1R_2CO + H_2C(CN)COOC_2H_5 \rightarrow R_1R_2C{=}C(CN).COOC_2H_5 + H_2O$$

With *cyclohexanone*, the reaction proceeds in the following manner[4]:



$$\underline{\overline{CH_2CH_2CH_2CH_2CH_2CO}} + H_2C(CN)COOC_2H_5 \rightarrow \overline{CH_2CH_2CH_2CH_2.CH{=}C}.CH(CN)COOC_2H_5 + H_2O$$

Cyanoacetic ester condenses with *acetone*, in the presence of ethylamine cyanoacetate, to form the compound: $(CH_3)_2C(CH_2CN).CH(CN).COOH$. Cyanoacetic ester reacts with *mesityl oxide* in the following manner[5]:

$$(CH_3)_2C{:}CH.COCH_3 + H_2C(CN)COOC_2H_5 \rightarrow \underset{(I)}{(CH_3)_2C{:}CH.C(CH_3){:}C(CN)COOC_2H_5}$$

$$(I) + H_2C(CN).COOC_2H_5 \rightarrow \underset{(II)}{(CH_3)_2C{:}CH.C(CH_3){:}C(CN).CO.CH(CN).COOC_2H_5} + HOC_2H_5$$

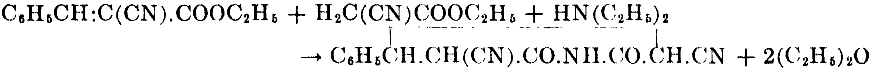
$$(II) + H_2O \rightarrow (CH_3)_2C{:}C(CN).CO.CH(CN).COOC_5H_5 + CH_3CO.CH_3$$

Oxomalonic ester condenses with methyl cyanoacetate to form dimethyl diethyl-1,3-dicyanopropane-1,3,2,2-tetracarboxylate, m.p. 114–115°[6]:

$$(C_2H_5OCO)_2CO + 2H_2C(CN).COOCH_3 \rightarrow (C_2H_5OCO)_2C[CH(CN).COOCH_3]_2 + H_2O$$

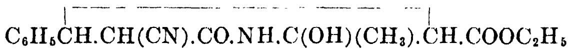
Oxalacetic ethyl ester condenses with ethyl cyanoacetate in the presence of pyridine, forming the compound $C_2H_5OCO.CH_2.C(COOC_2H_5){:}C(CN)COOC_2H_5$, needles, melting at 75°. Oxalacetic ethyl ester reacts with the sodium compound of ethyl cyanoacetate, giving, after treatment of the product of reaction with acid $C_2H_5OCO.CH{:}C(COOC_2H_5).CH.(CN)COOC_2H_5$. This compound has acid properties. It is transformed to aconitic acid upon treatment with hydrochloric acid; sulfuric acid transforms it to dihydroxycinchoueronic acid. Alcoholic potassium hydroxide, reacting with the compound, gives citrazinic acid, *i.e.* 2,6-dihydroxypyridine-4-carboxylic acid[7].

Benzaldehyde condenses with cyanoacetic ethyl ester to form benzylidene cyanoacetic ester[8], $C_6H_5CH{:}C(CN).COOC_2H_5$. This compound reacts with dimethylamine and ethyl cyanoacetate to give 2,6-diketo-3,5-dicyano-4-phenylpiperidine:



$$C_6H_5CH{:}C(CN).COOC_2H_5 + H_2C(CN)COOC_2H_5 + HN(C_2H_5)_2 \rightarrow C_6H_5CH.CH(CN).CO.NH.CO.CH.CN + 2(C_2H_5)_2O$$

When ethyl acetoacetate is used in this reaction in place of ethyl cyanoacetate, the compound formed is 2-methyl-3-carbethoxy-4-phenyl-5-cyano-6-ketopiperidine[9],

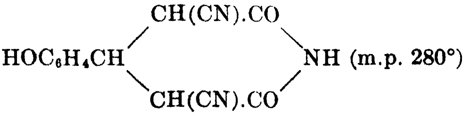


$$C_6H_5CH.CH(CN).CO.NH.C(OH)(CH_3).CH.COOC_2H_5$$

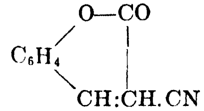
Cyanoacetic ethyl ester has been condensed with *o-nitrobenzaldehyde* to *o*-nitro-α-cyanocinnamic ester[10].

Phenylacetaldehyde reacts with cyanoacetic esters to form α-carbalkoxy-γ-phenylcrotonic nitriles, $C_6H_5CH_2CH{:}C(CN).COOR$. These compounds condense spontaneously upon distillation to 2-cyano-α-naphthol. Diphenylacetaldehyde reacts with ethyl cyanoacetate in the presence of diethylamine acetate to form β-benzhydrylglutaric acid, $(C_6H_5)_2CH.CH(CH_2COOH)_2$, m.p. 177.6–178.2°, in 12–21% yield[11].

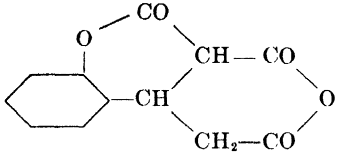
Salicylaldehyde condenses with ethyl cyanoacetate forming salicylidene bis(ethyl cyanoacetate): $HOC_6H_4CH[CH(CN)COOC_2H_5]_2.\frac{1}{2}H_2O$, m.p. 140°. Alcoholic ammonia reacts with this, forming an imido compound:



The potassium salt of the acid, $HOC_6H_4CH(CH(CN)COOK)_2$, is decomposed with dilute sulfuric acid forming cyanocoumarin[12]:



Treated with boiling dilute hydrochloric acid, salicylidines bis(ethyl cyanoacetate) gives the anhydride of β-*o*-hydroxyphenylpropane-α,α,γ-tricarboxylic acid[86],

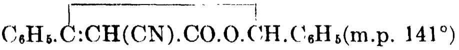


(m.p. 85–86°)

Products of condensation of *p*-aminobenzaldehydes with ethyl cyanoacetate. of the type $R_1R_2NC_6H_4CH{=}C(CN)COOEt$, have been proposed as dyestuffs. Dyestuffs have also been obtained through the condensation of such aldehydes with benzyl cyanide[124].

Phenylacetone reacts with ethyl cyanoacetate in the presence of piperidine to form γ-phenyl-β-methyl-α-carbethoxycrotonic nitrile, $C_6H_5CH_2C(CH_3){:}C(CN).COOC_2H_5$. This is transformed on heating at 240 to 250° for three hours, to 3-methyl-1-hydroxy-2-naphthonitrile, m.p. 202°[13].

Ethyl cyanoacetate has been condensed with *benzoin* to the lactone of α-cyano-β,γ-diphenyl-γ-hydroxycrotonic acid,



$C_6H_5.C{:}CH(CN).CO.O.CH.C_6H_5$(m.p. 141°)

The product has been obtained in a yield of 85% of theory[15]. *Benzil* reacts with ethyl cyanoacetate to form ethyl α-cyano-β-benzoylcinnamate[15], $C_6H_5C(COC_6H_5){:}CH(CN).CO_2C_2H_5$, m.p. 141°.

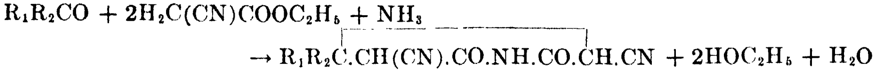
Ethyl acetoacetate has been condensed with ethyl cyanoacetate to ethyl α-cyano-β-methylgluconate[16], $C_2H_5OCO.CH(CN).C(CH_3){:}CH.COOC_2H_5$.

β-*Naphthaldehyde* condenses with ethyl cyanoacetate in the presence of morpholine to ethyl α-cyano-β-naphthylacrylate, m.p. 125–126°[17].

Isatin condenses with ethyl cyanoacetate to ethyloxindolylidenecyanoacetate, m.p. 202° and diethylindole-2,3-dicyanoacetate monohydrate, m.p. 99–100°[18].

Methyl ethyl ketone condenses with sodio ethyl cyanoacetate at elevated temperatures to the sodium derivative of 6-imino-1,2,4-trimethyl-4-ethyl-3-cyano-1-hexene-3-carboxylic ethyl ester. *Methyl propyl ketone* yields sodio-4-imino-1-cyano-2,6-dimethyl-5-ethylpropyl-5-cyclohexene-1-carboxylic acid ethyl ester; *diethyl ketone* forms sodio-α-cyano- β, β′-diethylacrylic ethyl ester; methyl hexyl ketone yields sodio-4-imino-1-cyan-2,6-dimethyl-5-amyl-2-hexyl-5-cyclohexene-1-carboxylic acid ethyl ester, and a product which, on distillation under vacuum, gives β-methyl-β-hexylacrylonitrile with liberation of carbon dioxide[19].

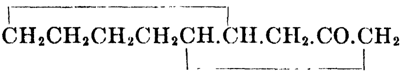
Cyanoacetic ester condenses with *aliphatic ketones*, R_1R_2CO, in the presence of ammonia to cyclic imides:



$$R_1R_2CO + 2H_2C(CN)COOC_2H_5 + NH_3 \rightarrow R_1R_2C.CH(CN).CO.NH.CO.CH.CN + 2HOC_2H_5 + H_2O$$

These compounds are known as "*Guareschi imides*"[20]. Upon hydrolysis with sulfuric acid, they are converted to β,β′-dialkylglutaric acids in excellent yield. This offers perhaps the best method for preparing the latter. The remaining hydrogen atoms in the ring may be readily replaced by bromine, and on boiling, bromine is removed, and spiro compounds with a three carbon ring result[21]. All ketones which give bisulfite compounds, and certain others which show no tendency to form such compounds, give *Guareschi bases* with ethyl cyanoacetate. Among the compounds of this type that have been prepared are those in which R_1 and R_2 are n-C_3H_7; CH_3 and $(CH_3)_2CH.$-CH_2, C_2H_5 and C_3H_7, CH_3 and $(CH_3)_2CH.(CH_2)_3$, CH_3 and $CH_3(CH_2)_5$, CH_3 and CH_3-$(CH_2)_8$ CH_3 and $C_6H_5CH_2.CH_2$, C_2H_5 and $C_6H_5CH_2CH_2$, C_3H_7 and $C_6H_5CH_2$.

Guareschi bases have also been made from *trans*- and *cis*-hexahydrohydrindones,



$$CH_2CH_2CH_2CH_2CH.CH.CH_2.CO.CH_2$$

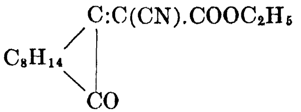
Acetaldehyde reacting with ethyl cyanoacetate in the presence of ammonia gives the ammonium salt of β,β-dicyano-γ-methylglutaconimine, m.p. above 310°, a small quantity of diethyl dihydrocollidinedicarboxylate, m.p. 130–131° and a compound of unknown structure melting at 210–212°[87]. Guareschi bases have been prepared from butyraldehyde[88], amisaldehyde and protocatechuic aldehyde[89]. Acetone reacting with ethyl cyanoacetate in the presence of ammonia gives a diacetoneamine which changes to a tetrahydropyridine derivative[90]; the N-methylated analog of the latter is obtained when the reaction is carried out in the presence of methylamine[91]. Methyl ethyl ketone reacting at 0° in the presence of ammonia gives the ammonia compound of β,β-dicyanomethylglutaconimine[92].

Acetylacetone and ethyl cyanoacetate heated in the presence of diethylamine react to form 2,4-dimethyl-5-carbethoxy-6-hydroxypyridine[93]. The nitrile of the corresponding carboxylic acid is obtained if the reaction is carried out in the presence of ammonia[94]. 2-Hydroxy-4-hexyl-6-methylnicotinonitrile results from the reaction of decane-2,4-dione, ethyl cyanoacetate and ammonia[95].

Benzaldehyde reacting with a mixture of ethyl cyanoacetate and ethyl acetoacetate in the presence of ammonia gives the ammonium compound of 2-methyl-4-phenyl-5-cyano-6-hydroxynicotinic acid[96].

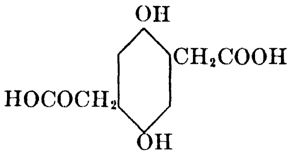
Ethyl cyanoacetate reacts at 20° with ethyl acetoacetate in the presence of ammonia forming 2,6-dihydroxy-4-methylnicotinonitrile. Similar compounds have been made from ethyl α-alkylacetoacetates[98], ethyl benzoylacetate[98], and diethyl acetosuccinate[99]. Ethyl cyanoacetamide gives 2,4-dimethyl-5,6-dihydroxynicotinonitrile with α-methylacetoacetamide and 2,6-dihydroxy-4-methyl-5-ethylnicotinonitrile with α-ethylacetoacetamide[97].

Phenylacetaldehyde reacts with sodio ethyl cyanoacetate in ethyl alcoholic solution to form, after hydrolysis, α,α′-dicyano-β-benzylglutaric acid, $C_6H_5CH_2$-$CH(CH(CN)COOH)_2$ m.p. 168°, and probably also ethyl α-cyano-β-benzyl-acrylate[22]. Furylcyanoacrylic ethyl ester has been prepared through the condensation of *furfural* and ethyl cyanoacetate[23]. *Camphorquinone* has been condensed with ethyl cyanoacetate to[24]:

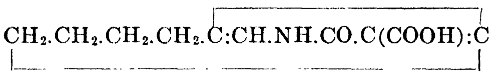


(m.p. 97°)

Ethyl cyanoacetate condensing with *benzoquinone* in the presence of ammonia forms a deeply colored crystalline compound[100]. Similar compounds are also obtained with cyanoacetamide and malononitrile[101]. These compounds are converted on hydrolysis to 2,5-dihydroxy-*p*-benzene diacetic acid,



1-Aminomethylene-2-cyclohexanone boiled with cyanoacetic ester in benzole solution in the presence of sodium powder four hours then allowed to stand twelve hours gives 3-ketotetrahydro*iso*quinoline-4-carboxylic acid[115],



$$CH_2.CH_2.CH_2.CH_2.C{:}CH.NH.CO.C(COOH){:}C$$

The condensation products of various ketones with ethyl cyanoacetate have been hydrogenated to the corresponding saturated α-cyano ester by treatment with moist aluminum amalgam[102].

Saturated α-cyano esters have also been obtained through the condensation of aldehydes or ketones with ethyl cyanoacetate and simultaneous catalytic reduction of the condensation product in the presence of palladized charcoal catalyst. Compounds of this type have been prepared by this method from acetaldehyde, propionaldehyde, butyraldehyde, *iso*butyraldehyde, *iso*valeraldehyde, haptaldehyde, benzaldehyde, acetone, methyl ethyl ketone, methyl propyl ketone, cyclohexanone, methyl *iso*butyl ketone, methyl amyl ketone, dipropyl ketone, methyl hexyl ketone. The reduction has been carried out under one to two atm. hydrogen pressure and at room temperature, except in the case of the condensation product with benzaldehyde, which required heating at 60°. The yields with few exceptions ranged between 70 to 90%, or over[103].

The β-hydrogen in α-cyanocrotonic acid, $CH_3CH.{=}C(CN)(COOCH_3$, may be replaced by a methyl group by reaction with diazomethane forming methyl *iso*propylidenecyanoacetate[104].

Condensations with Cyanoacetic Acid or its Salts

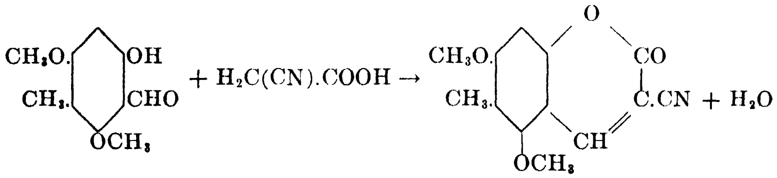
Crotonaldehyde may be condensed with cyanoacetic acid, in the presence of a base, to the salt of crotylidenecyanoacetic acid[25], $CH_3.CH{:}CH.CH{:}C(CN)COOH$.

Aromatic aldehydes condense with cyanoacetic acid in the presence of ammonia to form aryl-α-cyanoacrylic acids[105].

Anisaldehyde has been condensed with sodium ethyl cyanoacetate to sodium anisylcyanoacrylate[26], $p\text{-}CH_3OC_6H_5CH{:}C(CN)COONa$. *3-Methyl-4-methoxybenzaldehyde* has been similarly condensed with sodium cyanoacetate to the sodium salt of 3-methyl-4-methoxy-α-cyanocinnamic acid[27]. Piperonylcyanoacrylic acid has been obtained from *piperonal*[26,28]. Cinnamylcyanoacrylic acid, $C_6H_5CH{:}CH.CH{:}C(CN)COOH$, has been prepared from *cinnamic aldehyde* and cyanoacetic acid[29].

Cinnamylcyanoacrylic ethyl ester exists in two isomeric forms, one labile and the other stable. The stable form gives rise on polymerization to a cyclobutane derivative melting at 125°. The labile form preponderates when a large amount of the basic catalyst is used, and the reaction is carried out at a higher temperature. The stable form results when a small amount of the catalyst is employed, and the reaction is carried out at little above room temperature. The stable isomer may be converted to the labile form by subjecting an alcoholic solution of the compound to the action of light rays. The labile isomer may be reconverted to the stable form by radiation in the presence of iodine[125].

Cyanoacetic acid condenses in the presence of sodium hydroxide with 2-hydroxy-4:6-dimethoxy-5-methylbenzaldehyde to 5:7-dimethoxymethyl-3-cyanocoumarin in good yield[30]:



7-Hydroxy-5-methoxy-3-cyanocoumarin has been prepared similarly from 2,4-dihydroxy-6-methoxybenzaldehyde[31].

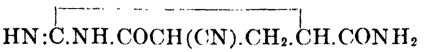
Arylidene cyanoacetic acids are readily reduced by sodium amalgam to the corresponding saturated acids[32]. Alkylidene cyanoacetic acids are not so reduced[33]. These compounds do not react with halogens, ozone and potassium permanganate[34].

p-Methoxybenzylidenecyanoacetic acid, $CH_3OC_6H_4CH{:}C(CN)COOH$, is oxydized with hypochlorous acid to p-methoxyphenylacetic acid, $CH_3OC_6H_4CH_2COOH$; aryl acetic acids are obtained similarly from o-methoxybenzylidene-, veratrylidene-, and piperonylidenecyanoacetic acids[106].

α-Cyanocrotonic acid, $CH_3CH{:}C(CN)COOH$, reacting with diazomethane gives methyl *iso*propylidenecyanoacetate, $(CH_3)_2C{:}C(CN)COOCH_3$, m.p. 19.5–21°[123].

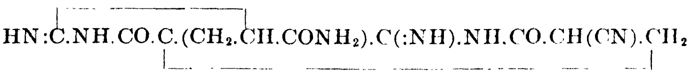
Condensations with Cyanoacetamide

Formaldehyde condenses with cyanoacetamide in weakly alkaline solution to form mono- and dimethylolcyanoacetamides, $H_2NCO.CH(CN).CH_2OH$, $H_2NCO.C(CN)(CH_2OH)_2$. α-Cyanoacrylamide, $CH_2{:}C(CN).CONH_2$, forms from the mono-compound by loss of one molecule of water. Cyanoacetamide, combining with one or two molecules of the mono-compound, gives methylene-bis-cyanoacetamide, $H_2NCO.CH(CN).CH_2CH(CN).CONH_2$, and dimethylene-tris-cyanoacetamide, $H_2NCO.CH(CN).CH_2C(CN)(CONH_2).CH_2CH(CN).CONH_2$, respectively. By internal condensation of these compounds, the cyclic amidines,



$HN{:}C.NH.COCH(CN).CH_2.CH.CONH_2$

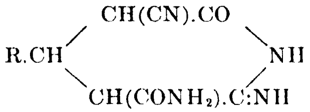
and



$HN{:}C.NH.CO.C.(CH_2.CH.CONH_2).C({:}NH).NH.CO.CH(CN).CH_2$

form[35].

Cyanoacetamide reacts with *acetaldehyde* and other higher aliphatic aldehydes to form the dicyanoglutaramides, $RCH[CH(CN).CONH_2]_2$, in good yield. These may form ring compounds of the type[36,37]:



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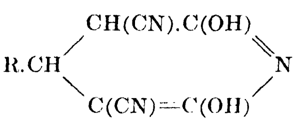
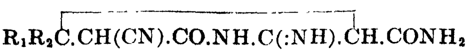


Cyanoacetamide reacts with *benzaldehyde* to form α-cyanocinnamic amide[38], $C_6H_5.CH{:}C(CN).CONH_2$. Other aromatic aldehydes react in a similar manner to form unsaturated α-cyanocarboxylamides[37,39]. *Phenylacetaldehyde* gives largely α-cyano-γ-phenylcrotonamide, $C_6H_5.CH_2CH{:}C(CN).CONH_2$, and a small quantity of benzyl dicyanoglutaramide[39], $C_6H_5CH_2.CH[CH(CN)CONH_2]_2$.

Ishag and Ray[41] condensed *cyanoacetanilide* and *cyanoacettoluide* with various aromatic aldehydes to substituted ω-cyanobenzylideneacetanilides, $RCH{:}C(CN)CONHR'$. The aldehydes employed were benzaldehyde, *o*-nitrobenzaldehyde, 3-methoxy-, 3,4-methoxybenzaldehyde, and 3,4-methoxy-6-nitrobenzaldehyde, piperonal and nitropiperonal. These compounds, on reduction with zinc dust and glacial acetic acid, gave 2-arylamino-3-cyanoquinolines. *Cyanoacetic arylamides*, $RNX.CO.CH_2CN$, have been condensed with aromatic aldehydes of the type, $R_2OCH_2CH_2.N(R_1).C_6H_4CHO$, in which R_1 and R_2 represent alkyl groups and from the condensation products, compounds of the general type; $R_2OCH_2CH_2N(R_1).C_6H_4CH_2CH(CN).CO.N(X)R$, have been obtained. These are dyes ranging in color from yellow to orange[42].

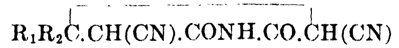
Furfural condenses with cyanoacetamide to α-cyano-β-furfuracrylic amide[23], $C_4H_3O.CH{:}C(CN)CONH_2$.

Ketones condense with cyanoacetamide in the presence of piperidine to six membered cyclic compounds,



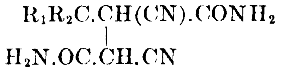
$R_1R_2C.CH(CN).CO.NH.C({:}NH).CH.CONH_2$

and



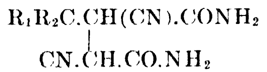
$$R_1R_2C.CH(CN).CONH.CO.CH(CN)$$

The first is formed by *trans* addition and predominates (95%), the second by *cis* addition. In the presence of ammonia, the second type of condensation products are formed. In the first stage of the reaction an unsaturated amide, $R_1R_2C{:}C(CN).CONH_2$, is formed which reacts with another molecule of cyanoacetamide to form the compounds:



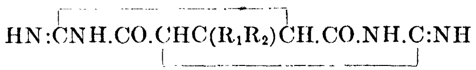
$$\begin{array}{l} R_1R_2C.CH(CN).CONH_2 \\ H_2N.OC.CH.CN \end{array}$$

and



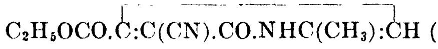
$$\begin{array}{l} R_1R_2C.CH(CN).CONH_2 \\ CN.CH.CO.NH_2 \end{array}$$

These then condense to the above cyclic compounds. There is also formed a dicyclic compound[43],



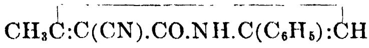
$$HN{:}CNH.CO.CHC(R_1R_2)CH.CO.NH.C{:}NH$$

Ethyl acetylpyruvate, $CH_3CO.CH_2CO.COOC_2H_5$, condenses with cyanoacetamide to 3-cyano-4-carbethoxy-6-methyl-2-pyridone,



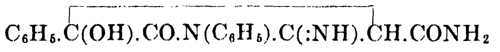
$$C_2H_5OCO.C{:}C(CN).CO.NHC(CH_3){:}CH$$ (m.p. 217–218°)

which may be converted to 2-chloro-6-methylpyridine-4-carboxylic acid. *Benzoylacetone*, $C_6H_5CO.CH_2.CO.CH_3$, condenses with cyanoacetamide to 3-cyano-6-phenyl-4-methyl-2-pyridone,



$$CH_3C{:}C(CN).CO.NH.C(C_6H_5){:}CH$$ (m.p. 182–183°)

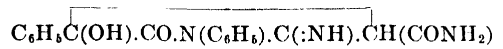
some 3-cyano-4-phenyl-6-methyl-2-pyridone, m.p. 249°, forming also. Propionylphenylacetylene, $CH_3CH_2.CO.C{:}C.C_6H_5$ reacts with cyanoacetamide to form 3-cyano-4-phenyl-6-ethylpyridone[44]. Cyanoacetamide condenses with benzoylformanilide, $C_6H_5.CO.CO.NHC_6H_5$, to the compound[45]:



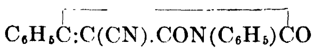
$$C_6H_5.C(OH).CO.N(C_6H_5).C({:}NH).CH.CONH_2$$

Cyanoacetamide condenses with *β-diketones* with varying degrees of ease according to the character of the radicals attached to the keto groups; the reaction is the more vigorous the lower the molecular weight of these groups. Benzoylacetophenone condenses with cyanoacetamide on three days' standing in the presence of diethylamine forming 3-cyano-4,6-diphenyl-2-pyridone, m.p. 320°, in 70% yield. 2-Benzoyl-*p*-methylacetophenone gives 3-cyano-4-phenyl-6-*p*-tolyl-2-pyridone, m.p. 267°, and 3-cyano-3-phenyl-6-*p*-tolyl-4-phenyl-2-pyridone, m.p. 240–242°. *Dipropionylmethane* gives with cyanoacetamide a crystalline compound which, when hydrolyzed with concentrated hydrochloric acid, forms 4,6-diethyl-2-pyridone, m.p. 61–62°[107].

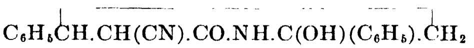
Benzoylformanilide, $C_6H_5CO.CO.NHC_6H_5$ condenses with cyanacetamide to 1,4-diphenyl-2-imino-3-formamido-4-hydroxy-5-pyrrolidone,


$$C_6H_5C(OH).CO.N(C_6H_5).C(:NH).CH(CONH_2)$$

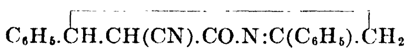
needles melting with decomposition at 209 to 210°. This compound is converted by phosphorus pentoxide to α-cyano-β-phenylmaleinanile[108],


$$C_6H_5C:C(CN).CON(C_6H_5)CO$$

Ethylideneacetone condenses with cyanoacetamide forming 2-keto-3-cyano-4,6-dimethyl-6-hydroxypiperidine and 2-keto-3-cyano-4,6-dimethyl-2,3,4,5-tetrahydropyridine, the second by the Michael condensation. *Mesityl oxide* gives with cyanoacetamide, 2-keto-3-cyano-4,4,6-trimethyl-6-hydroxypiperidine, colorless prisms melting at 273–276°. *Ethylideneacetophenone* gives 2-keto-3-cyano-4-methyl-6-phenyl-6-hydroxypiperidine and 2-keto-3-cyano-4-methyl-6-phenyl-2,3,4,5-tetrahydropyridine; *ethylidene-p-methylacetophenone* gives similar products. *Tetrahydroacetophenone* condensed with cyanoacetamide forms 1-methyl-3-keto-4-cyano-3,4,5,6,7,8,9,10-octahydro*iso*quinoline, short colorless needles melting at 358–360°[109]. The condensation product of cyanoacetamide and *benzalacetophenone*[110] appears to be the compound


$$C_6H_5CH.CH(CN).CO.NH.C(OH)(C_6H_5).CH_2$$

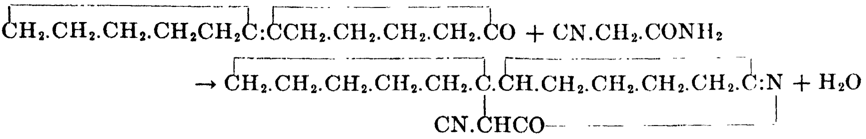
which on dehydration gives


$$C_6H_5.CH.CH(CN).CO.N:C(C_6H_5).CH_2$$

Similar compounds have been made through the condensation of cyanoacetamide with the *benzal ketones*, $C_6H_5CH:CH.CO.R$, in which R is CH_3, C_2H_5, $p\text{-}CH_3C_6H_4$[111].

Cyanoacetamide reacting at 0° with *hydroxymethyleneketones*, $RCO.CH:CHOH$, in dilute alcoholic solution in the presence of pyridine gives cyanopyridones. Thus a cyanopyridone is obtained in good yield from *hydroxymethylene-p-methylacetophenone;* 3-cyano-5-methyl-6-phenyl-2-pyridone is obtained from *hydroxymethyleneethyl phenyl ketone*, and 3-cyano-6-ethyl-2-pyridone from *hydroxymethylenemethyl ethyl ketone*. Hydroxymethyleneketones condensing with cyanoacetamide in the presence of sodium according to the Michael reaction give substituted 2,3,4,5-tetrahydropyridines. Thus, 2-keto-3-cyano-4-acetoxy-2,3,4,5-tetrahydropyridine is obtained from *hydroxymethyleneacetophenone*, and 2-keto-3-cyano-4-acetoxy-6-*p*-tolyl-2,3,4,5-tetrahydropyridine from *hydroxymethylene-p-methylacetophenone*[112].

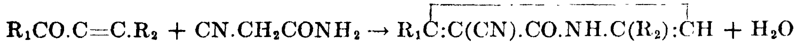
Copper compounds of hydroxymethyleneketones, $RCOCH:CHOH$, reacting with cyanoacetamide in dilute alcoholic solution at 0° and in the presence of pyridine give cyanopyridones. Thus copper oxymethylene-*p*-methylacetophenone forms 3-cyano-6-*p*-tolyl-2-pyridone, yellow needles melting at 278°–280°. The acetates of hydroxymethyleneketones give 2-keto-3-cyano-2,3,4,5-tetrahydropyridines on condensation with cyanoacetamide[113]. Cyanoacetamide condenses with *cyclohexylidenecyclohexanone* as follows:



$$CH_2.CH_2.CH_2.CH_2CH_2C:CCH_2.CH_2.CH_2.CH_2.CO + CN.CH_2.CONH_2 \rightarrow CH_2.CH_2.CH_2.CH_2.CH_2.C.CH.CH_2.CH_2.CH_2.CH_2.C:N + H_2O$$
$$CN.CHCO$$

4′-Methylcyclohexylidene-4-methylcyclohexanone and 3′-methylcyclohexylidene-3-methyl-6-cyclohexanone give similar condensation products[114].

Cyanoacetamide condensing with α-ketones of the acetylenic series forms cyanopyridones:



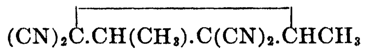
$$R_1CO.C\equiv C.R_2 + CN.CH_2CONH_2 \rightarrow R_1C:C(CN).CO.NH.C(R_2):CH + H_2O$$

Compounds in which R_2 is phenyl and R_1 the hydrocarbon residues C_6H_5, p-$CH_3.C_6H_4$, p-$NO_2.C_6H_4$, CH_3 and C_3H_7 have been prepared[116].

Condensations with Malononitrile

Malononitrile reacts with *formaldehyde* to form a number of condensation products, among them methylene-bis-malononitrile, $H_2C[CH(CN).CN]_2$, and pentane-1,1,3,3,5,5-hexanitrile[46], $(NC)_2C.[CH_2.CH(CN)_2]_2$.

Acetaldehyde gives with malononitrile, according to conditions, ethylidene-bis-malononitrile, $CH_3.CH[CH(CN)_2]_2$, or 1,3-dimethylcyclobutane-2,2,4,4-tetranitrile[47],

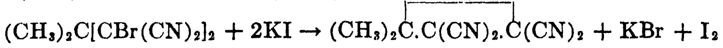


$$(CN)_2C.CH(CH_3).C(CN)_2.CHCH_3$$

Acetone condenses with malononitrile to methylethylidenemalononitrile, $(CH_3)_2C:C(CN)_2$, b.p.$_{23}$ 107–108°, which polymerizes on standing to a dimer[48]. Other ketones react in a similar manner to form unsaturated dinitriles[49].

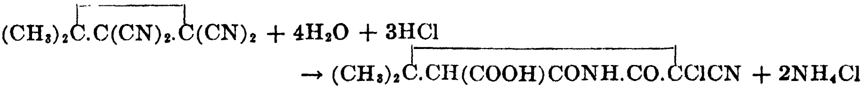
Acetone reacts at ordinary temperature with monobromomalononitrile in the presence of potassium iodide to form 2,2-dimethyl-1,1,3,3-tetracyanocyclopropane, m.p. 209.5–210°, in 70% yield[50].

$$(CH_3)_2CO + 2BrCH(CN)_2 \rightarrow (CH_3)_2C[CBr(CN)_2]_2 + H_2O$$



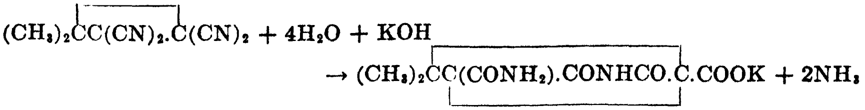
$$(CH_3)_2C[CBr(CN)_2]_2 + 2KI \rightarrow (CH_3)_2C.C(CN)_2.C(CN)_2 + KBr + I_2$$

The compound is hydrolyzed by concentrated hydrochloric acid at 100° as follows:



$$(CH_3)_2C.C(CN)_2.C(CN)_2 + 4H_2O + 3HCl \rightarrow (CH_3)_2C.CH(COOH)CONH.CO.CClCN + 2NH_4Cl$$

Alkali hydrolysis with 1 to 2 normal potassium hydroxide solution proceeds as follows:



$$(CH_3)_2CC(CN)_2.C(CN)_2 + 4H_2O + KOH \rightarrow (CH_3)_2CC(CONH_2).CONHCO.C.COOK + 2NH_3$$

Malononitrile condenses with *ethyl cyanoformate* in the presence of potassium ethoxide to potassium cyanoxymethylenemalononitrile[51]:

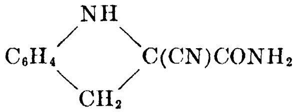
$$(CN)_2CH_2 + OC(CN).OC_2H_5 + KOC_2H_5 \rightarrow (CN)_2C{:}C(CN)OK + 2HOC_2H_5$$

A side reaction apparently also takes place resulting in the formation of potassium ethoxymethylenemalononitrile: $(CN)_2C{:}C(OC_2H_5)OK$.

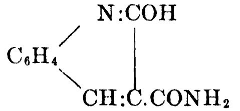
Malononitrile condenses with *ethyl oxalate* in the presence of potassium ethoxide to potassium-α-oxy-β,β-dicyanoacrylic ethyl ester[52]:

$$(CN)_2CH_2 + OC(OC_2H_5).COOC_2H_5 + KOC_2H_5 \rightarrow (CN)_2C{:}C(OK).COOC_2H_5 + 2HOC_2H_5$$

Benzaldehyde condenses with malononitrile to benzalmalononitrile, $C_6H_5CH{:}C(CN)_2$, m.p. 83.5–84°, a compound which exerts a tear and sneeze producing effect[53]. Other aromatic aldehydes react similarly, giving substituted styryldicyanides. Corson and Stoughton[53] prepared by this reaction hydroxy-, methoxy-, chloro-, and nitrostyryldicyanide; 3-methoxy-4-hydroxystyryl dicyanide, and 3,4-methylenedioxystyryl dicyanide. Kaufmann[54] prepared dimethoxystyryl dicyanides. *o*-Nitrostyryl dicyanide, $o\text{-}NO_2C_6H_4CH{:}C(CN)_2$, which may be obtained by the condensation of *o-nitrobenzaldehyde* and malononitrile, has been converted to an indole derivative,



by partial hydrolysis followed by reduction; a quinoline derivative,



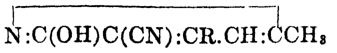
has been obtained from this[55].

Benzophenone reacts with malononitrile to form diphenyldicyanoethylene. *Benzoylformanilide* gives 1-phenyl-1-formanilido-2,2-dicyanoethylene[56], $C_6H_5C[{:}C(CN)_2]CONH.C_6H_5$. *Terephthaldehyde* condenses with malononitrile, normally, to form the corresponding unsaturated dinitrile[57].

Acetylacetone condenses with malononitrile to 3-cyano-ψ-lutidostyryl in 70% yield; *benzoylacetone* gives 3-cyano-4-methyl-6-phenyl-2-pyridone[107].

Benzoylformanilide, $C_6H_5CO.CONHC_6H_5$, reacts with malononitrile in the presence of diethylamine to form 1-phenyl-1-formanilido-2,2-dicyanoethylene, $C_6H_5NHOC(C_6H_5){:}C(CN)_2$, m.p. 206–207°. Hydrolyzed with hydriodic acid, this compound changes to the corresponding diamide[108].

Pyridine derivatives of the formula



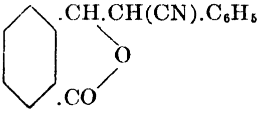
$$\overline{N{:}C(OH)C(CN){:}CR.CH{:}C}CH_3$$

in which R is CH_3 or an alkoxymethylene, may be obtained by condensing acetylacetones of the general formula, CH_3COCH_2COR, with malononitrile in the presence of a small quantity of ammonia or other nitrogenous bases[113].

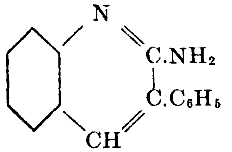
Condensations with Benzyl Cyanide and Other Condensations

Aromatic aldehydes do not all condense with benzyl cyanide with equal ease. Many react in the presence of sodium ethoxide. Salicylaldehyde and vanillin do not react at all[58].

Opianic acid (benzaldehyde *o*-carboxylic acid) has been condensed with benzyl cyanide to α-phenyl-β-*o*-carboxyphenylacrylonitrile and by further condensation to cyanobenzylphthalide[59]:

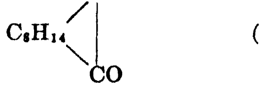


Benzaldehyde condenses with benzyl cyanide to form α-phenylcinnamonitrile[60], $C_6H_5CH{:}C(CN).C_6H_5$. The compound is reduced to $C_6H_5CH_2.CH_2C_6H_5$ and HCN. It may be condensed with a second molecule of benzyl cyanide to α,β,γ-triphenylglutaronitrile, $C_6H_5CH[CH(C_6H_5)CN]_2$, m.p. 138°. *o-Hydroxybenzaldehyde* has been condensed with benzyl cyanide to α-phenyl-*o*-hydroxycinnamonitrile, m.p. 104°, from which, on hydrolysis, α-phenylcoumarin, m.p. 140°, has been obtained[61]. *Para-methoxybenzaldehyde* condenses with benzyl cyanide in the presence of sodium ethoxide to 4-methoxy-α-phenylcinnamonitrile[62], $CH_3OC_6H_4.CH{:}C(CN).C_6H_5$. DeKiewiet and Stephen[63] prepared the condensation products of 4-hydroxy-2-methoxy-, 4-hydroxy-3-methoxy-2,4-dimethoxy-, 3,4-dimethoxy- and 2-methoxy-4-acetoxybenzaldehydes with benzyl cyanide. *Ortho*-nitrobenzaldehyde has been condensed with benzyl cyanide to 1-nitrophenylcinnamonitrile. Upon reduction of the nitro group in this compound, internal condensation takes place and Py-1-amino-Py-2-phenylquinoline,



forms[64].

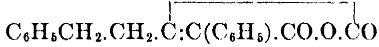
Benzophenone has been condensed with benzyl cyanide in the presence of sodium ethoxide to triphenylacrylonitrile, $(C_6H_5)_2C{:}C(C_6H_5)CN$. The yield of the product is poor[65]. Benzophenone reacting with sodiobenzyl cyanide, $CNCH(Na)C_6H_5$, gives the same compound. *p*-Methylbenzophenone and naphthyl phenyl ketone, $C_6H_5COC_{10}H_7$, react with sodiobenzyl cyanide in a similar manner[66]. Benzyl cyanide has been condensed with *furfural* to α-phenylfurfuracrylonitrile[67], $C_4H_3OCH{:}C(CN)C_6H_5$, m.p. 42–43°. *Camphorquinone* has been condensed with benzyl cyanide to[24]:



(m.p. 167°)

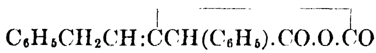
Added to an aqueous alcoholic solution of benzyl cyanide and potassium hydroxide cooled to 2°, *pyruvic acid* reacts to give the potassium salt of α-methyl-β-phenylmalic acid, $PhCH(CN).C(OH)(CH_3).COOH$, m.p. 128–130 (dec.) in 55% yield. The acid decomposes slowly in the cold to benzyl cyanide and pyruvic acid. Decomposition proceeds rapidly when the compound is heated in alkaline solution. Treated with a solution of hydrogen chloride in acetic acid, the compound is converted to phenylmaleic anhydride, m.p. 94.5°, and a nitrogenous body melting at 171.5°. The amide $PhCH(CONH_2)C(OH)(CH_3)COOH$, which is obtained by treatment of the cyano acid with cold, concentrated sulfuric acid, is converted on treatment with a solution of hydrogen chloride in acetic acid to a cyclic imide[40].

Benzyl cyanide condensing with *phenylpyruvic* acid gives the mononitrile of benzylphenylmalic acid, $C_6H_5C(CN):C(COOH).CH_2C_6H_5$, dec. above 160°. Concentrated solutions of alkalies reacting with this compound decompose it to benzyl cyanide and the alkali metal salt of phenylpyruvic acid[117]. With benzylpyruvic acid, benzyl cyanide forms a hydroxy nitrile which upon hydrolysis gives the unsaturated anhydride,



$$C_6H_5CH_2.CH_2.\overset{|}{C}:C(C_6H_5).CO.O.\overset{|}{C}O$$

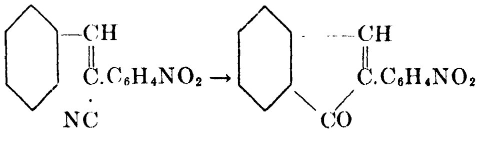
potassium hydroxide converts this to[118]



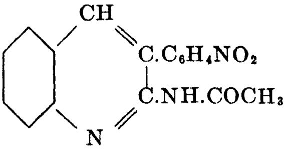
$$C_6H_5CH_2CH:\overset{|}{C}CH(C_6H_5).CO.O.\overset{|}{C}O$$

Substituted benzyl cyanides, in general, react with carbonyl compounds in the same manner as benzyl cyanide. Niederl and Ziering[68] have prepared substituted cyanostilbenes from *p*-methoxyphenylacetonitrile, 3,4-dimethoxy- and 3,4-dimethyleneoxyphenylacetonitriles and various aromatic aldehydes, in yields ranging between 30 and 40% of theoretical. *Para*-nitrophenylacetonitrile condenses with *p*-nitrobenzaldehyde to 4,4′-dinitro-7-cyanostilbene, $NO_2C_6H_4.CH:C(CN).C_6H_4NO_2$. The *meta*-nitro and *ortho*-nitro compounds react similarly. Thus, the compounds 3,3′-dinitro-, 2,2′-dinitro-, 4,3′-dinitro-[69] and 4,2′-dinitro-7-cyanostilbenes have been prepared. *p*-Nitrophenylacetonitrile has been condensed with *p*-nitrocinnamic aldehyde to di-*p*-nitrophenylcyanobutadiene[70], $NO_2C_6H_4.CH:CH.CH:C(CN)C_6H_4NO_2$. These nitro compounds have been reduced to the corresponding amino compounds. Tetrazo dyestuffs have been made from the *p*-amino compounds.

α-Phenylcinnamonitriles condense to phenylindone derivatives when heated with concentrated sulfuric acid[71]:

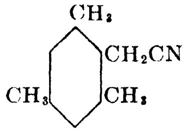


Pschorr[72] prepared *p*-nitrophenyl-*o*-acetaminocinnamic nitrile, $o\text{-}CH_3CONH.C_6H_4\text{-}CH:CH(CN)C_6H_4NO_2$, by condensing *o*-acetaminobenzaldehyde and *p*-nitrobenzyl cyanide. The compound is readily transformed to α-acetamino-(β)-p-nitrophenylquinoline,



p-Nitrobenzyl cyanide has been condensed with *furfural* to α-p-nitrophenylfurfuracrylonitrile[73], $C_4H_3OCH{:}C(CN)C_6H_4NO_2$, m.p. 114°. α-p-Aminophenylfurfuracylonitrile, $C_4H_3O.CH{:}C(CN)C_6H_4NH_2$, m.p. 111–112°, has been prepared from furfural and p-aminobenzyl cyanide[74].

Mesitylacetonitrile,



does not condense with formaldehyde, though the methylene group is capable of acylation to form compounds of the type, $(CH_3)_3C_6H_2CH(COR)CN$, and may be methylated and benzylated to the compounds $(CH_3)_3C_6H_2CH(CH_3)CN$ and $(CH_3)_3C_6H_2CH(CH_2C_6H_5)CN$.

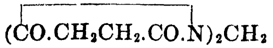
ω-Cyanoacetophenone has been condensed with *benzaldehyde* and various substituted benzaldehydes to benzal- or substituted benzalcyanoacetophenones, $RCH{:}C(CN).CO.C_6H_5$; and with *glyoxal*, forming 1,4-dicyano-1,4-dibenzoylbutadiene[75], $C_6H_5COC(CN){:}CH.CH{:}C(CN).COC_6H_5$. With *salicylaldehyde* in the presence of dry hydrogen chloride it forms 3-benzoylcoumarin, m.p. 138°, in 60% yield. *Ortho-* and *para*-bromosalicylaldehydes give 6-methyl- and 7-methyl-3-benzoylcoumarin respectively; resorcylaldehyde gives 6-hydroxy-3-benzoylcoumarin[120].

Sodium bromoacetate reacting with a mixture of potassium cyanide and benzaldehyde gives sodium cyanocinnamate; sodium chlorocyanoacetate does not form the cyanocinnamate under these conditions, but gives a mixture of other products[122].

An amido stilbene is also formed when 2-methyl-5-nitrobenzonitrile is made to react with benzaldehyde in the presence of sodium methoxide[83].

Chloral condenses with acetonitrile to form the compound[84], $Cl_3C.CH(CH_2CN)_2$.

Formaldehyde condenses with succinonitrile in acetic acid solution and in the presence of sulfuric acid, forming methylenedisuccinimide,



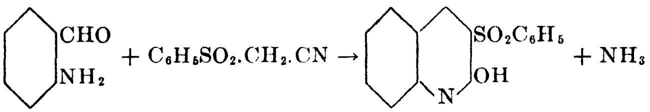
$$(\overline{CO.CH_2CH_2.CO.N})_2CH_2$$

Benzaldehyde, added to a cold alcoholic solution of succinonitrile containing sodium ethoxide and the mixture kept for two days at room temperature, forms a compound of the empirical formula $C_{21}H_{22}N_2O_2$, probably $C_6H_5CH(C_6H_5.C(OH)NH_2)_2$, m.p. 214°. If the mixture is heated, the compound, $CN.CH_2C({:}CH.$-

C_6H_5).$CONH_2$, m.p. 260°, forms. *Anisaldehyde,* reacting under the same conditions, gives: $CH_3OC_6H_5CH{:}C(CONH_2).CH_2.CONH_2$, m.p. 255°[12].

Condensations with Arylsulfonylacetonitriles

Arylsulfonylacetonitriles react with aromatic aldehydes to form unsaturated α-sulfonylnitriles[76], $RCH{:}C(SO_2R')CN$. The condensation of *o*-aminoaldehydes yields *o*-aminosulfonylcinnamonitriles, from which α-amino-β-sulfonylquinolines have been obtained[77]. If the reaction is carried out in a sealed tube at 170°, a substituted carbostyril forms with loss of ammonia:

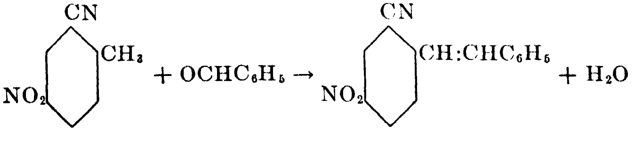


Upon reduction with tin and hydrochloric acid, the aminoquinoline gives tetrahydroquinoline and a thiophenol[78].

o-Nitrobenzaldehyde condenses with arylsulfonylacetonitriles in alcoholic solution in the presence of a little pyridine, forming *o*-nitrosulfonylcinnamonitriles. On reducing these compounds, aminosulfonylquinolines are obtained[79].

Arylsulfonylacetonitriles are converted by nitrous acid to oximes, $RSO_2C({:}NOH)CN$. The hydrogen of the oxime group is replaceable with alkyl groups. The two hydrogens in arylsulfonylacetonitrile are also replaceable with alkyl groups[121].

2-Methyl-5-nitrobenzonitrile condenses with benzaldehyde when heated at 120–140° in the presence of pyridine as a catalyst, forming 2-cyano-4-nitrostilbene[80]:



The compound reacts with various other aromatic aldehydes in a similar manner[81]. With *m*-methoxybenzaldehyde, 2-cyano-4-nitro-3-methoxystilbene is obtained in nearly quantitative yield when a mixture of the nitrile and aldehyde is heated at 150–160° in the presence of pyridine[82]. With *o*-nitrobenzaldehyde, reaction proceeds violently in the presence of piperidine, and minute quantities of stilbene are formed. Condensation proceeds well in the presence of sodium methoxide, but the reaction product is then the amidostilbene.

Properties of Various Condensation Products

In the following tables, some of the constants of condensation products obtained from various aldehydes and cyano compounds with an active methylene group are given, together with references to the original articles. The yields of the condensation products have been given whenever available.

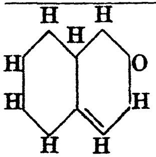
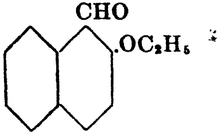
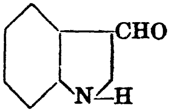
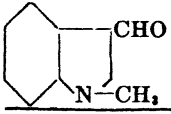
(1) **Condensations with Cyanoacetic Ester**

Condensation Products of Type $R_1R_2C:C(CN).COOR$

Carbonyl Compound Condensed with Cyanoacetic Ester	*R*	*Melting Point, etc. of Condensation Product*	*Yield of Condensation Product % of Theory*	*Reference*
$CH_3.CO.CH_3$	C_2H_5	.....	.....	I
	CH_3	m.p. 20.3°, b.p.$_9$ 99–101°	...	III
$CH_3.CO.C_2H_5$	C_2H_5	b.p.$_{11}$ 116–8°, $d/^{20}_4 = 1.0091$	65–85	II, IX
$CH_3CO.C_3H_7$	C_2H_5	b.p.$_{19}$ 136–9°, $d/^{20}_4 = 0.9899$	77–85	II, IX
$CH_3.CO.C_4H_9(n)$	C_2H_5	b.p.$_{19}$ 149–150°	85	II
	CH_3	b.p.$_9$ 105–106°	.....	III
$CH_3.CO.CH_2.CH(CH_3)_2$	CH_3	b.p.$_{12}$ 130–3°	75	II
$CH_3.CO.C_5H_{11}$	CH_3	b.p.$_2$ 124–5°	80	II
$CH_3.CO.CH_2.CH(CH_3).C_3H_7$	CH_3	b.p.$_9$ 119–123	....	III
$CH_3.CO.C_7H_{15}$	CH_3	b.p.$_9$ 139–141°	....	III
$CH_3.COC_8H_{17}$	CH_3	b.p.$_9$ 149–152°	.....	III
$C_2H_5.CO.C_2H_5$	C_2H_5	b.p.$_9$ 116–8°, $d/^{20}_4 = 0.9931$	55–65	II, IX
$C_2H_5.CO.C_3H_7$	C_2H_5	b.p.$_3$ 104.5°, $d/^{20}_4 = 0.9768$	....	IX
$C_2H_5CO.C_4H_9$	CH_3	b.p.$_9$ 112–114°	....	III
$C_6H_{13}.CHO$	C_2H_5	b.p.$_{13}$ 144–145°	32	X
$C_3H_7.CO.C_3H_7$	C_2H_5	b.p.$_{11}$ 136–137°, $d/^{20}_4 = 0.9630$	52	II, IX
$C_3H_7.CO.C_5H_{11}$	CH_3	b.p.$_9$ 129–130°	....	III
$(CH_3)_2CH.CH_2.CO.CH_2.CH(CH_3)_2$	C_2H_5	b.p.$_3$ 116–118°	< 5	II
n-$C_5H_{11}.CO.C_5H_{11}$	C_2H_5	b.p.$_1$ 138–139°	48	II
$\overline{CH_2.(CH_2)_3.CO}$	CH_3	m.p. 31°, b.p.$_9$ 140–141°	.....	III
	C_2H_5	.....	....	V
$\overline{CH_2(CH_2)_4.CO}$	C_2H_5	b.p.$_9$ 150–151°	83	II, VI
$\overline{CH_2.CH(CH_3).CH_2CH_2CO}$	C_2H_5	.....	.....	VIII

$CH:C(CH_3).(CH_2)_3.CO$	C_2H_5	b.p.$_{12}$ 178–190°	40	XII
$CH:C(CH_3).CH_2CH(CH_3).CH_2.CO$	C_2H_5	m.p. 57–58°, b.p.$_{16}$ 192–195°	..	XII
$CH_2(CH_2)_5.CO$	C_2H_5	b.p.$_{15}$ 160–163°	53	VII, X
$CH_3CO.CH_2COOC_2H_5$	C_2H_5	....	....	LX
$CH_3CO(CH_2)_2COOC_2H_5$	C_2H_5	.	.	LX
$CH_3COCH_2COCH_3$	C_2H_5	..	.	LX
$C_2H_5OCH_2COCH_2COCH_3$	C_2H_5	..	...	LX
o-HOC_6H_4CHO	C_2H_5	m.p. 162–163°	quantitative	XXXVII
3,4-$(HO)_2.C_6H_3.CHO$	C_2H_5	m.p. 168°	..	XI, XXXV
3,4,5-$(HO)_3.C_6H_2.CHO$	C_2H_5	m.p. 201–202°	.	XI
p-$CH_3OC_6H_4CHO$	C_2H_5	m.p. 85°	80–85	XLVI
3,4-$(CH_3O)(HO).C_6H_3.CHO$	C_2H_5	m.p. 107°		XXXV
2,4$(CH_3O)_2.C_6H_3.CHO$	C_2H_5	..	.	IV
3,4-$(CH_3O)_2C_6H_3.CHO$	C_2H_5	.	..	IV
3,4-$CH_2O_2:C_6H_3CHO$	......	.	.	XLVI
$C_6H_4CH:CH.CHO$	C_2H_5	m.p. 140°	.	XLVI
3,4-$CH_2O:H_2C_6Br(6).CHO$	C_2H_5	m.p. 131°	...	XIII
2,4-$[(CH_3)_2N]_2.C_6H_3.CHO$	C_2H_5	m.p. 110–112°	....	XXXIV
o-$NO_2.C_6H_4.CHO$	......	m.p. 96°	85	XXXVII
m-$NO_2.C_6H_4CHO$	C_2H_5	m.p. 127–128°	85–90	XXXVII
$C_6H_5.CO.CH_3$	C_2H_5	b.p.$_2$ 136–137°	60	II
$CH_3.C_6H_4.COCH_3$	C_2H_5	b.p.$_3$ 141–143°	47	II
$C_6H_5.CO.C_2H_5$	C_2H_5	b.p$_2$ 136–138°	73	II
$C_6H_5COC_3H_7$	C_2H_5	b.p.$_2$ 135–136°	78	II
$C_6H_5.CO.C_5H_{11}$	C_2H_5	b.p.$_1$ 146–148°	75	II
$C_6H_5CH_2CO.CH_3$	C_2H_5	b.p.$_1$ 139–140°	76	II
$C_6H_5.CH_2.CH_2CO.CH_3$	C_2H_5	b.p.$_3$ 167–168°	64	II
$C_6H_5.CO.C_6H_5$	C_2H_5	b.p. 195–200°	66	II
$C_6H_5CO.CO.C_6H_5$	C_2H_5	m.p. 141°	.....	XIV
$C_6H_5CH_2.CO.C_6H_5$	C_2H_5	m.p. 163°	.....	XXXVII

(1) Condensations with Cyanoacetic Ester (*Continued*)

Carbonyl Compound Condensed with Cyanoacetic Ester	*R*	*Melting Point, etc. of Condensation Product*	*Yield of Condensation Product % of Theory*	*Reference*
	C_2H_5	.....	.....	VIII
	C_2H_5	m.p. 71°	.....	XXXVI
$CH_2.CH_2.CH.C(CH_3).C(CH_3).CO.CH_2$	C_2H_5	.....	.....	XV
$OCH.C_6H_4.CHO$ (*p*)	C_2H_5	m.p. 201°	.....	XVI
$CH:CH.OCH(CHO):CH$	C_2H_5	.....	.....	XLV, XLVI
α-Ionone	CH_3	b.p.$_{1.5}$ 1575°–159.5	...	L
β-Ionone	CH_3	b.p.$_2$ 165–168°	.....	L
*Trans*hexahydrohydrindone	C_2H_5	.....	.....	LI
	C_2H_5	m.p. 165°	94	LXI
	C_2H_5	m.p. 150°	94	LXI

(2) Condensations with Cyanoacetic Acid or Its Salts

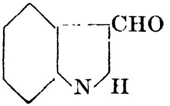
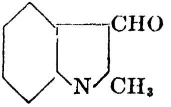
Condensation Products of Type $R_1R_2C{:}C(CN)COOH$

Carbonyl Compound Condensed with Cyanoacetic Acid or Its Salt	*Melting Point of Condensation Product,* * °C*	*Yield of Condensation Product % of Theory*	*Reference*
CH_3CHO	80	.....	XVII, XXXVIII
$CH_3.CH_2.CHO$	82–84	...	XVII
$(CH_3)_2CHCH_2CHO$	53	.....	XVII
$CH_3CH{:}CH.CHO$	....	.....	XL
$(CH_3)_2C{:}CH.CHO$	....	.	LXII
$(CH_3)_2C{:}CH.CH_2.CH_2C(CH_3){:}CH.CHO$-(citral)	.....	....	XLIV
β-Cyclocitral	....	....	LXII
$C_6H_{11}.CHO$	114	.....	X
$C_6H_5.CHO$	....	80–90	XVIII, XIII, XIX, XX, XXXIX
$CH_3O.C_6H_4CHO$	226	80–85	XVIII
3,4-$CH_2O_2{:}C_6H_3CHO$	228	95	XVIII
$C_6H_5CH{:}CH.CHO$	....	.....	XXI, XXII
$CH_2O_2C_6H_3.CHO$	....	...	XLVII
p-$(CH_3)_2CHC_6H_4CHO$	156.7	...	LVIII
2,3-$HO(CH_3O)C_6H_3CHO$	140–160	.....	LVIII
2,3-$(CH_3O)_2C_6H_3CHO$	222	.....	LVIII
2,3-$AcO(CH_3O)C_6H_3CHO$	180–181	....	LVIII
3,4-$(EtO)_2C_6H_3CHO$	178–179	....	LVIII
2,4,5-$Cl(CH_3O)_2C_6H_2CHO$	280	....	LVIII
$C_{10}H_7CHO(1)$	225	.....	LVIII
CH_3COCH_3	....	70	LV
$CH_3COC_2H_5$	....	70	LV
$CH_3COC_3H_7$	.....	70	LV
$CH_3COCH(CH_3)_2$	......	56	LV
$CH_3COC_4H_9$	......	61	LV
$CH_3COC_6H_{13}$	....	65	LV
$CH_3COCH{:}C(CH_3)_2$	.	70	LV
$CH_2.(CH_2)_3CO$	....	90	LV
$CH_2(CH_2)_4CO$	....	73	LV
$C_6H_4.CH_2.CH_2CO(\alpha)$	....	70	LV

* Melting points are those of free acid.

(3) Condensations with Cyanoacetamide

Condensation Products of Type $R_1R_2C:C(CN).CONH_2$

Carbonyl Compound Condensed with Cyanoacetamide	*Melting Point of Condensation Product, °C*	*Yield of Condensation Product % of Theory*	*Reference*
$(CH_3)_2CH.CHO$	151	79	XXIII
n-$C_6H_{13}.CHO$	197	. .	XXIII
$C_6H_5.CHO$	. . .	.	XXV
o-$HO.C_6H_4.CHO$	191 (dec.)		XXIII
$CH_3O.C_6H_4.CHO$	207	80	XXIII
3,4-$CH_2O_2:C_6H_3.CHO$	210	quantitative	XXIII
3,4,5-$(HO)_3C_6H_2.CHO$	268 (dec.)	. .	XI
3,4-$CH_3O(HO).C_6H_3.CHO$	209	. .	XXIII
$C_6H_5CH:CH.CHO$	161	80	XXIII
$CH:CH.O.CH:C.CHO$	. . . .	. .	XXIV
	243	90	LXI
	201–202	71	LXI

(4) Condensations with Cyanophenylacetamide

Condensation Products of Type $R_1R_2.C:C(CN).CONHC_6H_5$

Carbonyl Compound Condensed with Cyanoacetanilide	*Melting Point of Condensation Product, °C*	*Reference*
3-$CH_3OC_6H_4CHO$	141	XXV
3,4-$(CH_3O)_2C_6H_3.CHO$	168	XXV
3,4-$(CH_2O_2:)C_6H_3.CHO$	182	XXV
2-$NO_2.C_6H_4.CHO$	206	XXV
3,4-$(CH_3O)_2$-6-$(NO_2)C_6H_2.CHO$	227	XXV
3,4-(CH_2O_2)-6-$(NO_2).C_6H_2.CHO$	169	XXV

(5) Condensations with Cyano-*p*-Tolyl Acetamide

Condensation Products of Type $R_1R_2.C:C(CN).CONHC_6H_4.CH_3$-*p*

Carbonyl Compound Condensed with Cyano-p-Tolyl Acetamide	*Melting Point of Condensation Product, °C*	*Reference*
C_6H_5CHO	. . .	XXV
3-$CH_3O.C_6H_4CHO$	144	XXV
3,4-$(CH_3O)_2C_6H_3.CHO$	198	XXV
3,4-$(CH_2O_2)C_6H_3CHO$	183	XXV
2-$NO_2C_6H_4.CHO$	182	XXV
3,4$(CH_3O)_2.C_6H_2$-6-$(NO_2).CHO$	174	XXV
3,4(CH_2O_2)-6-$(NO_2).C_6H_2.CHO$	216	XXV

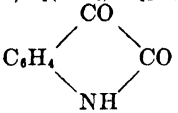
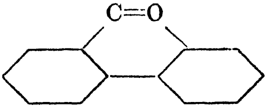
(6) Condensations with Malononitrile

Condensation Products of Type $R_1R_2C:C(CN)_2$

Carbonyl Compound Condensed with Malononitrile	*Melting Point, etc., of Condensation Product*	*Yield of Condensation Product % of Theory*	*Reference*
$(CH_3)_2.CO$	b.p.$_{23}$107–108°, d/$^{25}_{25}$ = 0.9541	. .	XXVI
$CH_3.CO.C_3H_7$	b.p.$_{12}$110–113°, d/$^{25}_{25}$ = 0.9294	. .	XXVI
$(C_2H_5)_2CO$	b.p.$_{23}$122–125°, d/$^{25}_{25}$ = 0.9311	. .	XXVI
$\overline{CH_2(CH_2)_4.CO}$	b.p.$_{10}$ 137–138° d/$^{25}_{25}$ = 1.0183	. .	XXVI
C_6H_5CHO	m.p. 83.5–84°	96	XXIV, XXVIII
p-$HO.C_6H_4.CHO$	m.p. 188.5–189.5°	77	XXVIII
o-$HO.C_6H_4.CHO$	m.p. 84–84.5°	. .	XXVIII
p-$CH_3OC_6H_4CHO$	m.p. 114.5–115°	93	XXVIII
3,5-$(HO)_2C_6H_3.CHO$	. . . .	. .	XXXIII
3,4-$(CH_3O)(HO).C_6H_3.CHO$	m.p. 133.5–134.5°	85	XXVIII
$(CH_3O)_2.C_6H_3.CHO$	. . . .	. .	XXVII
2,3-$(CH_2O_2)C_6H_3.CHO$	m.p. 199–200°	85	XXVIII
3,4,5-$(HO)_3C_6H_2.CHO$	m.p. 268° (dec.)	. .	XI
2,3,4-$(CH_3OCO)_3C_6H_2.CHO$	m.p. 139–140°	. .	XI
o-$Cl.C_6H_4.CHO$	m.p. 95–96°	85	XXVIII
m-$NO_2.C_6H_4CHO$	m.p. 104.5–105°	90	XXVIII,
p-$OCH.C_6H_4.CHO$*	m.p. 212° (dec.)	. .	XVI
$\overline{OCH:CH.CH:C}.CHO$	m.p. 72.5–73°	80	XXVIII, XXIV

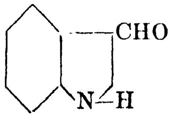
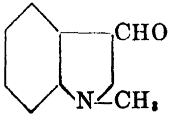
* Resulting product is $(CN)_2C:CH.C_6H_4CH:C(CN)_2$.

(6) Condensations with Malononitrile (*Continued*)

Carbonyl Compound Condensed with Malononitrile	*Melting Point, etc., of Condensation Product*	*Yield of Condensation Product % of Theory*	*Reference*
p-$(CH_3)_2N.C_6H_4.CHO$	m.p. 179–180°	..	XXXI, XXXIII
2,4-$[(CH_3)_2N]_2C_6H_3.CHO$	m.p. 166°	..	XXXIV
	m.p. 235°	..	XXXIII
$(C_6H_5)_2CO$	m.p. 136°	..	LI
	m.p. 213°	..	LI
$C_6H_5COCH_3$	m.p. 94°	70	LIX
p-$ClC_6H_4COCH_3$	m.p. 96°	75	LIX
p-$FC_6H_4COCH_3$	m.p. 122°	79	LIX
p-Xenyl acetophenone	m.p. 159°	74	LIX
p-$NO_2.C_6H_4COCH_3$	m.p. 154°	80	LIX
p-$C_2H_5OC_6H_4COCH_3$	m.p. 88°	78	LIX
p-$CH_3C_6H_4COCH_3$	m.p. 97°	85	LIX
2,4-$(CH_3)_2C_6H_3.COCH_3$	m.p. 87°	60	LIX
m-$C_2H_5C_6H_4.COCH_3$	m.p. 109°	79	LIX
p-$C_2H_5C_6H_4COCH_3$	m.p. 67°	60	LIX
p-$(CH_3)_2CH.C_6H_4COCH_3$	b.p.$_2$ 152–154°	63	LIX
p-$(CH_3)_3CC_6H_4COCH_3$	b.p.$_2$ 158–159°	67	LIX
3,5-$(C_2H_5)_2C_6H_3COCH_3$	m.p. 83–84°	60	LIX
α-Thienyl methyl ketone	m.p. 86°	71	LIX
$C_6H_5COC_4H_9$ (*n*)	m.p. 57	70	LIX
$C_6H_5COC_6H_{11}$ (*n*)	b.p.$_3$ 154–156	61	LIX

(7) Condensations with Benzyl Cyanide

Condensation Products of Type $R_1R_2C{:}C(CN).C_6H_5$

Carbonyl Compound Condensed with Benzyl Cyanide	*Reaction Product Melting Point, etc., of Condensation Product*	*Reference*
CH_3CHO	b.p. 244–246°	XLVIII
$C_6H_5.CHO$	m.p. 86°	XXXII
$CH_3C_6H_4CHO$	. . . .	XLIX
p-, *m*- and *o*-HOC_6H_4CHO	. . . .	XLIX
p-$CH_3OC_6H_4CHO$	m.p. 93°	XXXII, XLI, XLIII
m-$CH_3OC_6H_4CHO$	. . . .	XLIX
m-$C_2H_5O.C_6H_4CHO$	. . . .	XLIX
p-$(CH_3)_2NC_6H_4CHO$	m.p. 136°	XVI
p-$OCH.C_6H_4CHO$*	m.p. 242°	XVI
2,4-$(CH_3O)_2.C_6H_3.CHO$	m.p. 95°	XXX
3,4-$(CH_3O)_2C_6H_3.CHO$	m.p. 88°	XXX
2,4-$(CH_3O)(HO)C_6H_3CHO$	m.p. 195°	XXX
$CH_2O_2C_6H_3.CHO$	. . . .	XLIII
3,4-$(CH_3O)(HO)C_6H_3CHO$	m.p. 99°	XXX
2,4-$(CH_3O)(CH_3COO)C_6H_3.CHO$	m.p. 158°	XXX
o-$NO_2.C_6H_4CHO$	m.p. 127–128°	XXXII
m-$NO_2.C_6H_4.CHO$	m.p. 133–134°	XXXII, XLI
p-$NO_2.C_6H_4.CHO$	m.p. 117–118°	XXXII
(3)Br-(4)-$CH_3OC_6H_3CHO$	. . . .	XLIX
$C_4H_3O.CHO$	m.p. 42–43°	XLIX
$C_6H_5CH_2CO.C_6H_5$	m.p. 212°	XXXVII
$CH_2(CH_2)_3.CH_2.CO$	b.p.$_{10}$ 173–174°	XXXVII
	m.p. 185°	LXI
	m.p. 136–137°	LXI

* Product: dicyanodistyryl, $C_6H_5C(CN){:}CH.C_6H_4CH{:}C(CN)C_6H_5$.

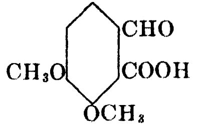
(8) Condensations with: (*a*) *p*-Methoxybenzyl Cyanide
(*b*) 3,4-Dimethoxybenzyl Cyanide
(*c*) 3,4-Methylenedioxybenzyl Cyanide
(*d*) *p*-Bromobenzyl Cyanide
(*e*) *p*-Nitrobenzyl Cyanide

Condensation Products of Type $R_1R_2C{:}C(CN)C_6H_4OCH_3$-*p*, $R_1R_2C{:}C.CN.C_6H_4Br$, $R_1R_2C{:}C(CN)C_6H_4NO_2$

Carbonyl Compound Condensed with Cyanide	*Melting Point, °C*					*Reference*
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	
$C_6H_5.CHO$	94	87	125	....	....	XXIX
				111–112	....	XLI
p-$CH_3.C_6H_4CHO$	97	112	122	....	......	XXIX
o-$CH_3O.C_6H_4.CHO$	98	87	102	....	. ....	XXIX
p-$CH_3O.C_6H_4.CHO$	108	129	129	....	....	XXIX
3,4-$(CH_3O)_2C_6H_3.CHO$	105	155	144	....	....	XXIX
2,4-$(CH_3O)_2C_6H_3.CHO$	...	...	...	....	....	XXIX
3,4-$(CH_2O_2{:})C_6H_3.CHO$	129	150	185	... ...	....	XXIX
o-$Cl.C_6H_4.CHO$	129	113	135	.....	.. ...	XXIX
p-$ClC_6H_4.CHO$	110	115	130	.. ....	.... ..	XXIX
m-$NO_2.C_6H_4.CHO$	159	166	195	....	199–200	XXIX, LIII
p-$(CH_3)_2N.C_6H_4CHO$	149	121	169	... ...	....	XXIX
$C_6H_5.CHO$	...	...	..	111–112	....	XXXII
$C_4H_3CO.CHO$	...	...	...	65	....	XXXII
p-$CH_3O.C_6H_4CHO$	. .	...	..	....	135	XXXII
2,4-$[(CH_3)_2N]_2C_6H_3.CHO$	...	...	..	... ...	170	XXXIV

(9) Condensations with *o*-Carbethoxybenzyl Cyanide, $C_2H_5OCOC_6H_4CH_2CN$

Condensation Products of Type $RCH{:}C(CN).C_6H_4.COOC_2H_5$ (Reference LII)

Carbonyl Compound Condensed with Cyanide	*Melting Point, °C*
C_6H_5CHO	163 (dec.)
p-$CH_3.C_6H_4.CHO$	151
m-$HO.C_6H_4.CHO$	160
o-$NO_2.C_6H_4CHO$	190
o-$Cl.C_6H_4CHO$	182
m-$Cl.C_6H_4.CHO$	148
p-$Cl.C_6H_4.CHO$	182
	

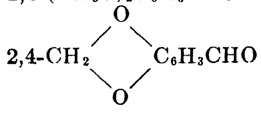
(10) Condensations with Arylsulfonacetonitriles RSO_2CH_2CN

Condensation Products of Type $R_1CH{:}C(CN).SO_2.R$

Carbonyl Compound Condensed with Cyanide	*Melting Point, °C*				*References*
	R = C_6H_5	*p-$CH_3C_6H_4$*	*BrC_6H_4*	*β-$C_{10}H_7$—*	
$C_6H_5.CHO$	135	114	119	122	LVI
o-HOC_6H_4CHO	160	152	143	173	LVI
p-$CH_3OC_6H_4CHO$	113	110	146	117	LVI
p-$NO_2.C_6H_4.CHO$	159	195	210	187	LVI
$C_6H_5CH{:}CH.CHO$	146	*oil*	176	157	LVI
p-HOC_6H_4CHO	....	...	....	...	LVII
p.$(CH_3)_2N.C_6H_4.CHO$	194	...	240–241	...	LVII
p-*iso*-$C_3H_7.C_6H_4.CHO$	78	...	166	. .	LVII
	R = p-$Cl.C_6H_4$	*p-$I.C_6H_4$*	*α$C_{10}H_7$*		
p-$HO.C_6H_4.CHO$	....	. .	157	...	LVII
p-$(CH_3)_2N.C_6H_4.CHO$	245–246	222	146	...	LVII
p-*iso*-$C_3H_7.C_6H_4.CHO$	154–156	...	197	...	LVII

(11) Condensations with Cyanoacetophenone

Condensation Products of Type $R_1R_2C{:}C(CN).CO.C_6H_5$

Carbonyl Compound Condensed with Cyanoacetophenone	*Product M.P., °C*	*Reference*
$C_6H_5.CHO$	84	XVI
p-$CH_3O.C_6H_4CHO$	104	XVI
p-$NO_2.C_6H_4.CHO$	140	XVI
p-$(CH_3)_2N.C_6H_4CHO$	162	XVI
p-$OCH.C_6H_4.CHO$	224	XVI
3,4-$(CH_3O)_2C_6H_3CHO$	...	IV
2,4-$(CH_3O)_2C_6H_3CHO$	...	IV
 2,4-$CH_2\langle O_2 \rangle C_6H_3CHO$	...	IV
3,4-$(CH_3O)(HO)C_6H_3CHO$	...	IV

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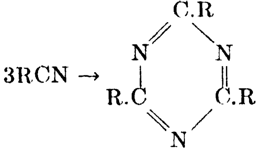
Chapter 17

Polymerization of Nitriles

The nitrile group being of an unsaturated character is highly reactive. The ready hydrolysis of nitriles to carboxylic acids, the formation of imino ethers, esters, and other transformations, in which the nitrogen to carbon bonds are involved, are indicative of this reactivity. Reactivity is evidenced also by the tendency of many nitriles to polymerize under the influence of certain reagents. This tendency is shown by all types of nitriles, though the polymeric compounds differ in type depending upon the type of nitrile, and the conditions under which polymerization takes place. In many instances, nitriles polymerize to form a trimolecular cyanuric ring compound:



Polymerization takes place in this manner only when no CH or CH_2 group is attached to the CN-group; as is the case with cyanogen halides, cyanoformic ester, benzonitrile, trichloro- and tribromo-acetonitrile and thiocyanic esters.

Polymerization of Hydrocyanic Acid

While pure hydrocyanic acid or hydrocyanic acid to which a small amount of a strong acid has been added is quite stable, hydrocyanic acid containing a small quantity of an alkaline substance polymerizes more or less rapidly, depending on the concentration of the alkaline compound and on the temperature.

Polymerization apparently takes place in stages, a dark brown substance, which remains in solution in hydrocyanic acid, forming at first. This intermediate compound probably exerts a catalytic influence on the polymerization. The process is accompanied by evolution of considerable heat, and if large quantities of liquid polymerize in a closed container, an explosion may ensue, caused by the great increase in the vapor pressure of hydrocyanic acid due to the rise in temperature. The final crude product is a dark, almost black, coal-like solid which cannot be reconverted to monomeric hydrocyanic acid.

The dark polymerization product apparently is a mixture of several chemical entities. Bedel isolated four fractions, differing in solubility in methyl cyanide, ether and water. The fraction soluble in methyl cyanide and ether, forming 2% of the total, contained a crystalline compound. Crystalline compounds could not be isolated from the other fractions. The reported analyses of the product are not in agreement, but it appears certain that the compound contains varying quantities of oxygen in addition to carbon, hydrogen and nitrogen[1].

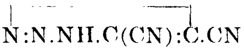
The Tetramer of Hydrocyanic Acid. The crystalline compound present in the dark polymerization product of hydrocyanic acid was first isolated by Salomone (l.c.) and was shown by Bedel (l.c.) to be a tetramer of hydrocyanic acid, a colorless solid, melting at 179° with decomposition, and stable at ordinary temperature. Bedel assigned to the compound the structural formula, $CN.CH(CN).NH_2.HCN$. Gryszkiewicz-Trochimowski considered the compound to be diaminomaleic dinitrile, $H_2NC(CN){:}C(CN).NH_2$. Hinkel and co-workers[2] regarded this formula incorrect and proposed the formula $H_2NCH(CN).C(CN){:}NH$.

The composition of the dark polymer of hydrocyanic acid varies to a considerable extent, according to conditions; the amount of the tetramer found in the product also varies. Under certain conditions, little or none of the tetramer forms and under other conditions, the quantity formed may be as much as 25% of the total polymerization product. The best yields seem to be obtained when the liquid is allowed to polymerize partially.

Linstead and co-workers[3] prepared the tetramer in the following manner:

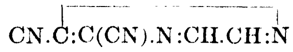
To 238 grams of anhydrous hydrocyanic acid was added 1 gram of potassium cyanide, and the liquid was maintained at a mean temperature of 10°. After the lapse of 3 days, the unpolymerized liquid was decanted off into another vessel and allowed to polymerize for 3 days and again the liquid was decanted and the process was repeated until polymerization was complete. Polymerization proceeded at the rate of 6 grams per day in the beginning and about half this rate toward the end. The combined yield of polymerization product was 190 grams. Extraction with ether yielded 33 grams of crude tetrameride. Because of the low solubility of the tetramer, extraction is a very slow process and the above quantity of the polymer was obtained after 3 days of extraction.

The tetramer gives with nitrous acid dicyanotriazole,



$$N{:}N.NH.C(CN){:}C.CN$$

which, on hydrolysis with sulfur dioxide, gives the corresponding dicarboxylic acid. With glyoxal, unsymmetrical dicyanopyrazine is formed,



$$CN.C{:}C(CN).N{:}CH.CH{:}N$$

and with δ-camphorsulfonic acid in acetic acid solution, aminoiminosuccinonitrile-δ-sulfonate is formed. The tetramer acts as a monoacid base.

Bimolecular Hydrocyanic Acid. A compound with the empirical formula $C_2H_2N_2$ has been prepared from formamino ether in ethereal solution by the action of solid sodium hydroxide. The structural formula $HN{:}CH.NC$ has been assigned to this compound[4]. The same compound has been made from thioformamide or its hydrate by heating in vacuum to 80°[5]. The compound melts at 81° and boils at 120–125°. Dilute acids or alkalies decompose it immediately into ammonia and formic acid. Hydrochloric acid, conducted into an ethereal solution of the dimer, converts it to dichloromethylformamidine hydrochloride, which precipitates out[6]. The formation of chloromethyleneformamidine, NH:-

CH.N:CHCl, from the compound, by the action of hydrogen chloride, has also been reported[7].

Aluminum chloride combines with hydrocyanic acid to form the double compound[7,8], $AlCl_3.2HCN$, m.p. 125° (dec.), also obtained by the interaction of aluminum chloride and iminoformyl carbylamine. It combines with hydrogen chloride to form a product which is identical with the compound obtained by the interaction of aluminum chloride and chloromethylene formimidine. The formula, $AlCl_3.NH:CHN:CHCl$, has been assigned to it. This complex is assumed to be the reactive unit in the Gattermann's aldehyde synthesis involving the use of hydrocyanic acid in the presence of aluminum chloride[9].

Trimer of Hydrocyanic Acid. A trimer of hydrocyanic acid, $H_2NCH(CN)_2$, has been isolated from the solid products obtained by exposing a mixture of hydrocyanic acid and epichlorhydrin to the action of sun's rays[10]. The trimer has also been isolated from the solid polymerization product deposited from an aqueous solution of hydrocyanic acid containing an alkali hydroxide or carbonate in solution[11].

The compound may be obtained in pure form by extracting the solid polymerization product with ether, evaporating off the ether, and crystallizing the residue from hot water after decolorization with animal charcoal. The trimer is obtained from alcohol in triclinic crystals which become brown at 140° and melt at 180°. At higher temperatures, the compound gives off hydrocyanic acid and decomposes with explosive puffs. It combines with hydrochloric acid to an amorphous, black compound, $(HCN)_3.3HCl.3H_2O$, which, on standing in a desiccator, changes to[12] $(HCN)_3.HCl$.

Hydrocyanic acid polymerizes to a dark, reddish solid when exposed to the action of alpha particles. Small amounts of hydrogen and nitrogen are liberated during the transformation. Cyanogen also polymerizes under the influence of alpha particles[13].

Polymerization of Aliphatic Nitriles

Unlike hydrocyanic acid, which may, under certain conditions, polymerize on storage at ordinary temperature, saturated aliphatic nitriles are comparatively stable and do not usually undergo any appreciable change on storage. These nitriles may be polymerized by the action of metallic sodium. Dimolecular or trimolecular nitriles are obtained, depending upon the conditions. Meyer[14] found that only primary nitriles, *i.e.*, nitriles in which the CN-group is attached to a CH_2-group, are capable of forming polymers.

Schwarze[15] caused the polymerization of nitriles with the sodium compounds of various alcohols and found that good yields of the trimers were obtained when sodium methylate was used in connection with acetonitrile, and sodium ethylate in connection with propionitrile. The trimers of alkyl cyanides are strongly basic compounds.

Methyl cyanide may be condensed under the action of sodium to a dimer, diacetonitrile, $CH_3C(NH_2):CH.CN$ or $CH_3.C(:NH).CH_2.CN$ m.p. 52°. Holtzwart[16] prepared the compound in the following manner:

Ten grams of sodium were thinly cut and placed in absolute ether and 25 grams of carefully dried methyl cyanide were added. The flask was cooled at first to prevent too vigorous a reaction, then heated to 40° under good agitation. The precipitate was filtered, washed with ether, then added to a small quantity of water. The oil that separated was allowed to crystallize, filtered, washed with water and dried. The yield was 70–80%.

The reactions involved are assumed by Holtzwart to be:

$$2CH_3CN + 2Na \rightarrow NaCH_2CN + CH_4 + NaCN$$
$$CH_3CN + NaCH_2CN \rightarrow CH_3C(NH_2){:}CNa.CN$$
$$CH_3C(NH_2){:}CNa.CN + H_2O \rightarrow CH_3C(NH_2){:}CH.CN + NaOH$$

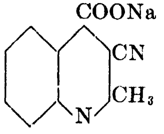
Moir[17] showed that diacetonitrile forms in almost quantitative yield from acetonitrile, without the use of a diluent, providing sodium is present in excess.

Diacetonitrile gives with benzoyl chloride a dibenzoyl derivative, $C_6H_5CO.N{:}C(CH_3).CH(CN).COC_6H_5$, m.p. 158°. Under the action of boiling water, diacetonitrile changes to a compound of unusual stability, the empirical formula of which is $C_8H_{18}ON_2$. Moir[17] considered it to be either 3-cyano-ψ-lutidostyrol or its polymer.

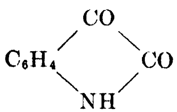
Diacetonitrile condenses with benzaldehyde in the cold, forming benzylidene-di(aminocrotonic nitrile), or its tautomer. $C_6H_5CH[CH(CN).C({:}NH).CH_3]_2$, m.p. 190°. Concentrated hydrochloric acid causes the condensation of this to 1,4-dihydro-4-phenyl-2,6-dimethyl-3,5-dicyanopyridine,

$$C_6H_5CH.C(CN){:}C(CH_3).NH.C(CH_3){:}C(CN) \quad (\text{m.p. } 204\text{–}206°)$$

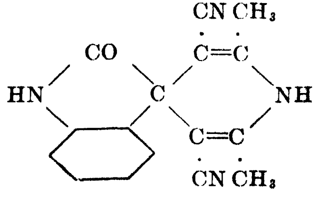
Similar condensation products are obtained from anisaldehyde. Condensation products have also been prepared with *p*-nitrobenzaldehyde and with piperonal. Salicylaldehyde, reacting with diacetonitrile in acetic acid, gives two products[18], $C_{15}H_{13}N_2O$ and $C_{18}H_{14}N_2O_2$. With the sodium salt of *o*-aminobenzoic acid, diacetonitrile gives the salt of α-methyl-β-cyanocinchoninic acid[19]:



With isatin,

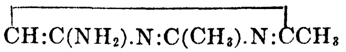


diacetonitrile forms the compound[19]:



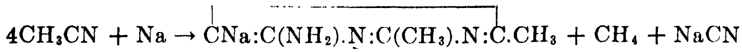
Other condensation reactions have been carried out with diacetonitrile and other dinitriles; these have been considered in the chapter dealing with condensation reactions.

Cyanmethin, or aminodimethylmiazin,



$$CH:C(NH_2).N:C(CH_3).N:CCH_3$$

is obtained when methyl cyanide is treated under a slight pressure, with 1/6 its weight of sodium[21]:

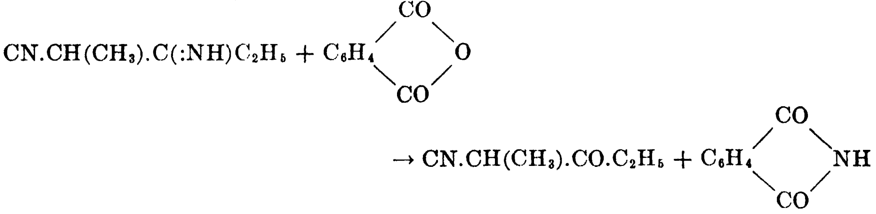


$$4CH_3CN + Na \rightarrow CNa:C(NH_2).N:C(CH_3).N:C.CH_3 + CH_4 + NaCN$$

The first stage of the reaction is probably the formation of diacetonitrile; evidence to this effect is found in the fact that cyanmethin results from the reaction of sodium diacetonitrile and methyl cyanide. Reaction proceeds to completion when the mixture is heated for four hours at 140°[22].

Cyanmethin combines readily with bromine to form bromocyanmethin; with chlorine chlorocyanmethin dichloride forms. The bromine in bromocyanmethin is not readily replaceable with other negative groups[23].

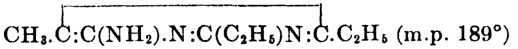
The dimer of *ethyl cyanide*, $C_2H_5C(:NH).CH(CH_3)CN$, m.p. 44–46° has been prepared from ethyl cyanide[24,34]. With benzoyl chloride the dimer forms a monobenzoyl derivative, $CN.C(CH_3).C(C_2H_5):N.COC_6H_5$, m.p. 198°; it also forms an acetyl derivative with acetyl chloride. The dimer reacts with phthalic anhydride to form α-cyanodiethyl ketone,



$$CN.CH(CH_3).C(:NH)C_2H_5 + C_6H_4\left\langle {CO \atop CO} \right\rangle O \rightarrow CN.CH(CH_3).CO.C_2H_5 + C_6H_4\left\langle {CO \atop CO} \right\rangle NH$$

Phenylhydrazine displaces the imino group in dimeric ethyl cyanide to form the compound $CN.CH(CH_3).C(C_2H_5):N.NH.C_6H_5$. Other dimeric nitriles react similarly[25].

Cyanethin, or aminomethyldiethylmiazen,



$$CH_3.C:C(NH_2).N:C(C_2H_5)N:C.C_2H_5 \text{ (m.p. 189°)}$$

was first prepared by Kolbe and Frankland[27]. Meyer[28] prepared the compound by the following method:

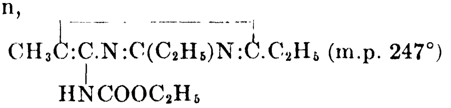
> One part by weight of sodium was placed in a flask protected from the moisture of the air, and 3 parts of anhydrous ethyl cyanide were added; additional 5 to 6 parts of anhydrous ethyl cyanide were then added gradually so as to prevent too rapid a reaction. After all the ethyl cyanide had been introduced, the mass was heated in an oil bath until all the sodium disappeared. The unreacted ethyl cyanide was then distilled off and the residue was cooled to solidification. The solid was broken up, washed with water and purified by crystallization from alcohol. The yield was 55 to 65% of the theoretical. Cyanethin is very slightly soluble in water, and fairly soluble in alcohol.

Sodium reacts vigorously at room temperature with ethyl cyanide in solution in

absolute ether to form sodium ethyl cyanide, $CH_3CHNaCN$, and sodium cyanide in equivalent quantities. Water decomposes this compound to an oil which crystallizes on standing, and melts at 47–48°, and boils at 257–258°, Metallic sodium reacts with this, giving sodium cyanide and cyanethin[29].

The structure of cyanethin was established by Meyer[30] who demonstrated that the compound was aminomethyldiethylpyrimidine.

Unlike cyanmethin, which combines readily with bromine, cyanethin reacts only upon heating with the halogen in a sealed tube for some hours, to form a monobromide. With chlorine, in the absence of water, a trichloride forms; iodine gives a monoiodide[31]. The bromine in bromocyanethin is readily replaced by other radicals[23]. Cyanethin reacts with ethyl chlorocarbonate to form carbethoxycyanethin,

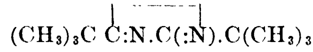


$$CH_3C{:}\underset{HNCOOC_2H_5}{C}.N{:}C(C_2H_5)N{:}C.C_2H_5 \quad (\text{m.p. } 247°)$$

an intensely bitter compound. From this, an anilide, m.p. 184°, has been prepared[32].

The dimers of *propylcyanide*[33], iminobutyrylcyanopropyl, butyl cyanide[34], capronitrile[33], and iminocaproylcapronitrile have been prepared from the monomeric nitriles. The trimers of propyl-, *iso*butyl- and *iso*amyl cyanides have also been prepared[14,35].

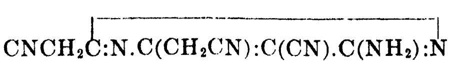
Phenylacetonitrile condenses under the action of sodium to the sodio derivative of a dimer, β-imino-α-cyano-α,γ-diphenylpropane[36], $C_6H_5CH_2.C({:}NH).CH(C_6H_5).CN$. *Trimethylacetonitrile* or *tert.*-butyl cyanide polymerizes to a dimer[37]:



$$(CH_3)_3C\ C{:}N.C({:}N).C(CH_3)_3$$

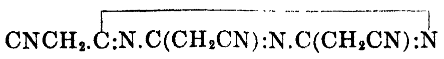
Sodium reacts with *iso*propyl cyanide, $(CH_3)_2CHCN$, in ether solution forming, after decomposition of the sodio derivative first formed, aminomethyl*iso*propylmiazin, m.p. 153–154°[38].

Malononitrile polymerizes in the presence of sodium ethoxide and other basic substances. Two types of polymers have been identified, both trimers. One melting at 290°, is soluble in pyridine but insoluble in most other solvents, and forms when sodium ethoxide or diethylamine is used as a polymerizing agent. The other melting at 218°, forms when ammonia is added to a benzol solution of the nitrile. It is soluble in water, acetone, alcohol and acetic acid. It is unstable above its melting point. The structure of these polymers has not been determined; the following are considered as the probable formulas[39]:



$$CNCH_2C{:}N.C(CH_2CN){:}C(CN).C(NH_2){:}N$$

and



$$CNCH_2.C{:}N.C(CH_2CN){:}N.C(CH_2CN){:}N$$

Mixed Polymers. Mixed polymeric nitriles result when mixtures of different nitriles are made to condense under the action of metallic sodium. *Cyanmethethin,*

$C_8H_{13}N_3$, m.p. 165–166°, has been prepared in this manner from a mixture of two moles of ethyl cyanide and one of methyl cyanide[40].

Mixed polymers have also been prepared from aromatic and aliphatic nitriles. Thus, 2-imino-2-phenylpropionitrile has been prepared from a mixture of acetonitrile and benzonitrile by the action of metallic sodium[22]. Attempts to cause acetonitrile to react with phenylacetonitrile have not met with success.

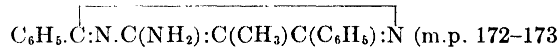
Iminobenzylcyanethyl, $C_6H_5(:NH).CH(CH_3).CN$ m.p. 97°, in the form of its sodium compound, results from the reaction of equimolecular quantities of benzonitrile and propionitrile in the presence of metallic sodium. *p*-Toluacetodinitrile, *p*-tolupropiodinitrile, diphenylacetodinitrile and benzophenacetodinitrile[41], as well as *ortho*-, *para*- and *meta*-benzoacetodinitriles, *p*-ethoxy- and *p*-dimethylaminobenzoacetodinitriles[20] have also been prepared. Sonn[26] prepared *p*-methoxyphenylacetodinitrile from *p*-methoxybenzonitrile and acetonitrile. When condensed with phloroglycinol, the dinitrile gives 5,7-dihydroxy-4-methoxyphenylcoumarin.

Meyer prepared iminobenzylcyanethyl in the following manner:

Twelve grams of propionitrile and 21 grams of benzonitrile were dissolved in absolute ether and 4.5 grams of metallic sodium were added. After the reaction was over, water was added and the mixture stirred. The semi-solid product which separated out was filtered and pressed between plaster plates, and was purified by dissolving in ethyl acetate and precipitating by the addition of petroleum ether[42].

Dilute hydrochloric acid converts the compound to α-cyanoethyl phenyl ketone, $C_6H_5CO.CH(CH_3)CN$. Boiled with water, it is gradually decomposed into ammonia and propionyl cyanide and some hydrocyanic acid; a product possessing a vigorous reducing power is formed at the same time which may be hydroxy diethyl ketone.

Cyanodiphenylethin,



$$C_6H_5.C:N.C(NH_2):C(CH_3)C(C_6H_5):N$$

(m.p. 172–173°)

has been prepared by heating the crude product of reaction of sodium with propionitrile in ether solution, with an equal weight of benzonitrile at 150° for three hours. This compound possesses strong basic properties. Heated with hydrochloric acid, it is converted to hydroxymethyldiphenylmiazin[42], $C_{17}H_{14}N_2O$, m.p. 256°.

Nitriles of the type, $RC(NH).C(R')(R'')CN$, may be prepared from the sodium compound of the mixed polymers, $R.C(:NH).CH(R')CN$, and alkyl iodides, $R''I$. Bouveault[43] prepared ketonitriles from these iminonitriles by hydrolysis with hydrochloric acid. Ketonitriles of this type are not attacked by alcoholic potassium hydroxide at boiling temperature; hydrochloric acid decomposes them slowly at 100°; and rapidly and completely at 140 to 150°, forming the ketone $RCO.CH(R')R''$.

Polymers of Halogenated Nitriles

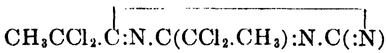
Dichloroacetonitrile saturated with hydrochloric acid and heated for several hours at 130 to 140° in a sealed tube condenses to a trimer. Under the same conditions, *trichloroacetonitrile* also polymerizes, though very slowly, but monochloroacetonitrile does not form a polymer[44].

Weddige[45] prepared the *trimer of trichloroacetonitrile* by saturating the nitrile with hydrochloric acid and exposing the solution in sealed tubes to the action of sunlight for a period of nine months. At the end of this time, the compound was completely solidified and the pure trimer was obtained by a single crystallization from alcohol. Tscherwen-Iwanoff[46] prepared the compound by saturating pure trichloroacetonitrile with hydrobromic acid and allowing the solution to stand in a closed container for two days. A crystalline product which formed at first disappeared, then the trimer began to form.

The trimer of trichloroacetonitrile crystallizes in large prisms, melting at 96°. It is very soluble in alcohol, ether, carbon disulfide and chloroform; very slightly soluble in water. It is volatile with steam. Water, hydrochloric and sulfuric acids are without action at 150 to 170°; concentrated hydrochloric acid decomposes it slowly at 200° with the formation of carbon dioxide and ammonium chloride. Alcoholic potassium hydroxide decomposes the trimer of trichloroacetonitrile to chloroform and potassium cyanurate; cold aqueous or alcoholic ammonia gives bis-(trichloromethyl)-aminotriazine, $(CCl_3)_2C_3N_3.NH_2$. Alcoholic ammonia reacts with the trimer, at 105–110°, to form trichloromethyldiaminotriazine, $Cl_3C.C_3N_3.(NH_2)_2$. Heated with aqueous ammonia in a sealed tube at 120° for 6 hours, the trimer gives diaminohydroxytriazine, $(NH_2)_2C_3N_3.OH$. With alcoholic ammonia, the latter is formed at 160 to 170°[45].

Broche[47] prepared the trimer of tribromoacetonitrile, m.p. 129–130°, following the procedure of Weddige. Hydrobromic acid failed to induce polymerization. This author prepared derivatives of the trimer of the type: $(CBr_3)_2C_3N_3X$, $CBr_3.C_3N_3.X_2$; $X = NH_2$, $NHCH_3$, $NH.C_6H_5$, and $(CBr_3)_2C_3N_3.OH$. Broche considered the trimer to be *sym.*-tris-(tribromomethyl)-triazine.

Otto and Voight[48] obtained a solid polymer during the chlorination of propionitrile, from which they claimed to have obtained, on reduction, *sym.*-triethyltriazine, m.p. 193–195°. These authors believed that the trimer has the structure:



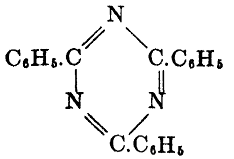
$CH_3CCl_2.C{:}N.C(CCl_2.CH_3){:}N.C({:}N).CCl_2CH_3$

Tröger[49] obtained, by reduction of the trimer, first a trichloro derivative, then finally cyanethin and a base of the formula, $C_9H_{15}N_2$. A dimer of α-dichloropropionitrile is also known[50].

Polymerization of Aromatic Nitriles

Benzonitrile and other aromatic nitriles form polymers, but while aliphatic nitriles yield pyrimidine derivatives, the polymers of aromatic nitriles contain the 1,3,5-triazine ring.

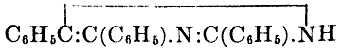
Benzonitrile condenses under the action of sulfuric acid or alcoholic hydrochloric acid to *cyaphenin:*



This compound was first prepared by Gloëz[51].

Cyaphenin is best prepared by adding benzonitrile to chlorosulfonic acid, $ClSO_3H$, and holding the solution at 0° for 24 to 48 hours. The yield is 40% of the theoretical[52]. Sulfuryl chloride and thionyl chloride do not induce polymerization. Cyaphenin has been obtained through the interaction of cyanogen bromide with benzene in the presence of anhydrous aluminum chloride at 50°[53]. Benzimino methyl ether, C_6H_5-(:NH)OCH_3, decomposes on long standing to methyl alcohol and cyaphenin[54].

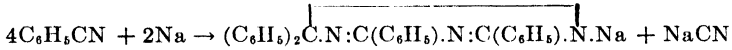
Cyaphenin may be nitrated to a trinitro derivative[55]. Reduced with zinc dust in warm glacial acetic acid, cyaphenin gives lophin[56],



$$C_6H_5C{:}C(C_6H_5).N{:}C(C_6H_5).NH$$

Cyaphenin may be hydrolyzed to benzoic acid[57].

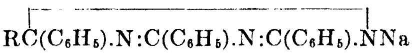
Metallic sodium causes the polymerization of benzonitrile in boiling benzene solution, the product formed being 1-sodio-2,2,4,6-tetraphenyl-1,2-dihydro-1,-3,5-triazine:



$$4C_6H_5CN + 2Na \rightarrow (C_6H_5)_2C.N{:}C(C_6H_5).N{:}C(C_6H_5).N.Na + NaCN$$

Metallic lithium acts in the same manner[58].

Anker and Cook[59] showed that organo-alkali compounds, RNa, react with benzonitrile at ordinary temperature to form compounds of the general type:

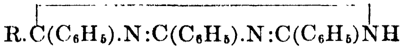


$$RC(C_6H_5).N{:}C(C_6H_5).N{:}C(C_6H_5).NNa$$

The melting points of the various compounds prepared by these authors are given in the following table:

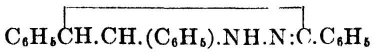
R	*M.P.* °*C*
Methyl	143
Ethyl	155
Propyl	116
*Iso*propyl	184
Butyl	117
Phenyl	192
Benzyl	251
Diphenylmethane	213

Benzonitrile reacts with alkyl lithium compounds, RLi, forming:



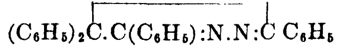
$$R.C(C_6H_5).N{:}C(C_6H_5).N{:}C(C_6H_5)NH$$

Benzyl lithium forms



$$C_6H_5CH.CH.(C_6H_5).NH.N{:}C.C_6H_5$$

and sodiodiphenylmethane yields

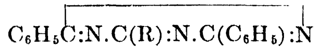


$$(C_6H_5)_2C.C(C_6H_5){:}N.N{:}C\ C_6H_5$$

on reaction with benzonitrile[59].

Cinnamylidenebenzyl cyanide in benzene or chloroform solution polymerizes in direct sunlight to a dimer melting at 94°. On heating an acetic acid solution of this compound to boiling an isomeric dimer melting at 215° is formed. Both dimers are depolymerized on treatment with concentrated sulfuric acid[131].

Condensation of Acyl Chlorides with Benzonitrile. Aliphatic acid chlorides, R.COCl, have been condensed with benzonitrile in the presence of aluminum chloride to diphenylalkyltriazines[60]:

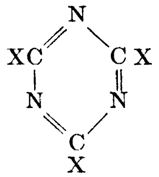


$$C_6H_5C{:}N.C(R){:}N.C(C_6H_5){:}N$$

Eitner and Kraft[61] condensed benzoyl chloride with benzonitrile in the presence of aluminum chloride and proved the formation of the compound $C_6H_5CCl{:}N.$-$C(C_6H_5){:}N.CO.C_6H_5.AlCl_3$. Cyaphenin was obtained from this by reaction with ammonium chloride in more than 60% yield.

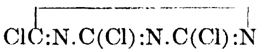
Polymerization of Cyanogen Halides

Cyanogen halides, X.CN (X = Cl, Br, I), polymerize to trimeric compounds of the type:



Polymerization generally occurs in the presence of halogen acids and is accelerated by heat.

Cyanuric chloride,



$$ClC{:}N.C(Cl){:}N.C(Cl){:}N$$

was first prepared by Serullas[62] who obtained it through the action of chlorine on anhydrous liquid hydrocyanic acid in direct sunlight. Gautier[63] prepared the compound by passing chlorine into a solution of hydrocyanic acid in chloroform which contained a small amount of alcohol. Hantzsch and May[64] prepared it by adding cyanogen chloride to a saturated solution of hydrochloric acid in ether.

Klason[65] prepared cyanuric chloride by passing chlorine for 4 to 5 hours into a well-cooled solution of hydrocyanic acid in chloroform, to which 1% ethyl alcohol was added, and allowing the solution to stand twelve hours in a freezing mixture, then distilling off the unconverted cyanogen chloride and the solvent. A maximum of 130 grams cyanuric chloride was obtained from 85 grams of hydrocyanic acid.

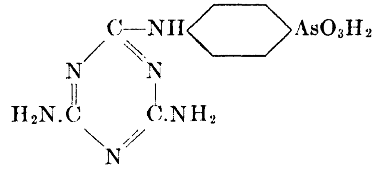
Cyanuric chloride is a solid crystallizing in the monoclinic system and possessing a characteristic sharp odor. It melts at 145° and boils at 190°. It is soluble in chloroform, carbon tetrachloride, anhydrous alcohol and acetic acid[66].

Cyanuric chloride, placed in contact with water, is gradually converted to cyanuric acid; it dissolves in aqueous solutions of alkalies forming the alkali metal salt of cyanuric acid, from which cyanuric acid may be liberated by the addition of a strong mineral acid. Cyanuric acid is depolymerized on heating to cyanic acid. This offers a convenient method for the preparation of pure *cyanic acid*[67].

Diels[68] attempted to reduce cyanuric chloride without success. He succeeded however, in reducing the mono- and diamino-derivatives, $NH_2C_3N_3Cl_2$ and $(NH_2)_2C_3N_3Cl$ to the corresponding hydrogenated compounds, $NH_2C_3N_3H_2$ and $(NH_2)_2C_3N_3H$.

Reactions of Cyanuric Chloride. The chlorine atoms in cyanuric chloride are reactive and may be replaced by various negative groups; they may be replaced, for example, by amino-[69] or substituted amino-groups[70]. One chlorine atoms is replaced most readily, the second less readily and the third with still greater difficulty. In general, mono-substituted amino compounds predominate in the reaction product when amines are made to react with cyanuric chloride at 0°, di-substituted compounds form principally in the temperature range 40 to 60° and tri-substituted compounds at 90 to 100°. With excess of amine, disubstituted compounds form in the cold.

Banks and co-workers[133] prepared the chloro-diamino compound in good yield by using a large excess of ammonia and carefully controlling the temperature conditions, starting the reaction in the cold and then gradually raising the temperature to 40°. Good yields of other diaminochlorotriazines may be obtained under similar conditions with other amines. The chlorine in chlorodiaminotriazine may be replaced with amino groups by reaction with the amino compound in slightly acid solution. Thus *p*-(2,4-dichloro-*s*-triazinyl-6)-aminophenylarsonic acid,



has been obtained in 96% yield by refluxing for 30 minutes a suspension of 43.8 grams of chlorodiaminotriazine in a liter of hot water to which were added 5 cc of concentrated hydrochloric acid, 2 cc of octyl alcohol and 65 grams of 4-aminobenzenearsonic acid[133]. This compound has enhanced trypanocidal and spirochetocidal activity and is highly effective against the micro-organism causing the African sleeping sickness[134].

Strong ammonia, heated in a closed vessel with cyanuric chloride, gives a nearly quantitative yield of melamine, which may be obtained in pure form by simply washing with water to free the product of the ammonium chloride formed, and crystallizing the melamine once from hot water[71].

Cyanuric chloride, heated at 100° with an ethereal solution of ethylamine, forms triethylmelamine, needles, m.p. 73°, very soluble in alcohol and ether. Triphenylmelamine has been obtained by heating aniline in excess with an ethereal solution of cyanuric chloride at 150°. The compound crystallizes in plates, m.p. 225°, subliming at 360°; hydrochloric acid decomposes it at 200° into aniline and cyanuric acid. tri-*p*-tolyl-, tri-3-amino-4-methylphenyl- and tri-α-and-β-naphthylmelamine have been prepared in a similar manner[72,73]. Tri-substituted melamines have also been made from cyanuric chloride and dimethylamine hydrochloride and free diethylamine[73].

Mosher and Whitmore[136] prepared the following substituted triazines from cyanuric chloride: chloroamino-3-piperidinopropylamino-, m.p. 178°; dichloro-3-piperidinopropylamino- m.p. 90°; amino-bis-3-piperidinopropylamino-, m.p. 78–80°; diamino-3-piperidino-, m.p. 163–164°; diamino-2-diethylaminopropylamino-, m.p. 132.8°; diamino-4-diethylaminobutylamino-, m.p. 241°; diamino-6-aminohexylamino-, m.p. 154°; diaminoethoxy-, m.p. 152.5–153.5°.

Hydrazine hydrate reacting with cyanuric chloride in solution in a mixture of alcohol and acetonitrile gives trihydrazine triazine[185].

Cyanuric chloride has been made to react with polymeric ethylenediamine, forming products which have been proposed as textile assistants. The polyamine residue in these compounds may be converted to quaternary ammonium compounds.

Tri-substituted cyanomelamines have been prepared from cyanuric chloride and mono-substituted alkali cyanamides[74]:

$$C_3N_3Cl_3 + 3NaN(CN).R \rightarrow C_3N_3[N(CN)R]_3 + 3NaCl$$

Cyanuric triazide, $C_3N_3(N_3)_3$, has been obtained from cyanuric chloride and sodium azide[75].

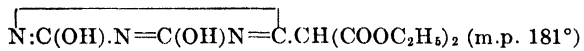
Sodium alcoholates and alkali metal salts of phenol react with cyanuric chloride to form the esters of cyanuric acid. Reaction also takes place with mono- and diamidocyanuric chloride, forming amido cyanuric esters[76].

Ethyl and methyl esters of cyanuric acid are depolymerized by heating under vacuum. The ethyl ester yields cyanic acid and ethylene; the methyl ester, which breaks down with greater difficulty, gives methyl *iso*cyanate[77].

Cyanuric chloride, heated with the dry alkali metal salts of organic acids, gives sodium cyanurate and the chloride of the acid[78]:

$$3R.COONa + Cl_3C_3N_3 \rightarrow 3RCOCl + (NaO)_3C_3N_3$$

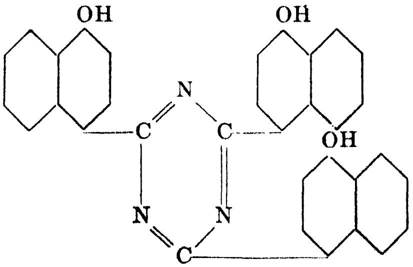
Reacting in alcoholic solution with sodio ethyl malonate, cyanuric chloride forms the compound:



$$\overline{N:C(OH).N{=}C(OH)N{=}C}.CH(COOC_2H_5)_2 \text{ (m.p. 181°)}$$

which may be decarboxylated to the monocarboxylic ester by heating in a sealed tube with concentrated hydrochloric acid to 130° for three to four hours[79,80].

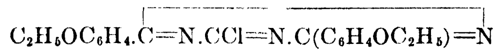
Phenolic compounds reacting with cyanuric chloride give hydroxy aryl triazines; thus, with α-naphthol, tris-hydroxynaphthyltriazine,



is formed[81].

Sodium sulfide reacts readily with cyanogen chloride to form sodium thiocyanurate[82], $(NaSCN)_3$.

Reacting with monobromobenzene in anhydrous ether solution and in the presence of metallic sodium, cyanuric chloride forms cyaphenin and diphenylcyanuric chloride[80], $(C_6H_5)_2(CN)_3Cl$. Cyanuric chloride reacts with *p*-bromophenol in ethereal solution in the presence of metallic sodium forming a mixture of di-(ethoxyphenyl)-chlorotriazine,



$$C_2H_5OC_6H_4.C{=}N.CCl{=}N.C(C_6H_4OC_2H_5){=}N$$

m.p. 149° and triethoxycyaphenin, m.p. 171°[132].

Reaction products of aromatic sulfonated amides and amines with cyanuric chloride have been proposed as tanning agents[137].

Dyestuffs from Cyanuric Chloride. A number of dyestuffs have been synthesized by the condensation of chromophoric groups with cyanuric chloride. These are prepared, in general, either by uniting intermediate products containing the triazine nucleus or by uniting dyes containing appropriate groupings by reaction with triazine halides.

A series of satisfactory green dyes have been prepared by linking together blue and yellow dye components through the cyanuric ring. *Chlorantine Fast Green BLL* is probably the best known of these dyes. *Chlorantine Fast Rubine RLL* is the condensation product of cyanuric chloride, aniline and a soluble complex of *ortho*-hydroxy azo-dyes[83]. Dyestuffs have also been made by condensing cyanuric chloride with aniline and 2-aminoanthraquinone, or with *m*-(chlorosulfuryl)-benzoic acid, or *p*-chlorobenzoyl chloride[84].

Cyanuric bromide forms when impure cyanogen bromide is heated to 130–140° alone or in ether solution[85]. It has been prepared directly from anhydrous hydrocyanic acid and bromine[86]. Cyanuric bromide also forms through the condensation of cyanogen bromide in ethereal solution in the presence of bromine or preferably hydrobromic acid[87].

Cyanuric bromide occurs as an amorphous powder, melting above 300°. It cannot be distilled without decomposition and is insoluble in cold water, absolute alcohol. benzene and ether. It decomposes in moist air to cyanuric acid and hydrogen bromide,

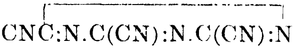
All bromine atoms in cyanuric bromide may be replaced upon reaction in benzene solution with a primary base, and certain secondary bases. Triaminomelamine $(CNNHNH_2)_3$ and triphenylaminomelamine $(CNNH.NHC_6H_5)_3$ have thus been prepared from cyanuric bromide and hydrazine and phenylhydrazine respectively. The following compounds have also been prepared by this method:

	M.P. °C
Tri-*o*-chlorophenylmelamine	161
Tris-(dichlorophenyl)melamine	261
Tris-(trinitrophenyl)melamine	
Tri-α-naphthylmelamine	225
Trimethylphenylmelamine	115
Tribenzylphenylmelamine	120

Benzidine and *p*-phenylene diamine replace all bromine atoms; *p*-aminophenol, *p*-anisidine and aminobenzoic acid replace two atoms of bromine. Trichloroaniline and dinitroaniline do not react. With tertiary bases very unstable addition products form[88]. Tricarbamylmelamine, $(NCNHCONH_2)_3$, has been made by reacting cyanuric bromide with urea at 130 to 140°.

Cyanuric iodide was prepared by Klason[89] through the interaction of cyanuric chloride and hydriodic acid in the cold, a small amount of cyanuric chlorodiiodide forming at the same time. It is a dark brown powder, insoluble in ordinary solvents, which decomposes when heated above 200° to paracyanogen and iodine.

Cyanuric cyanide or hexacyanogen,



$$\mathrm{CNC{:}N.C(CN){:}N.C(CN){:}N}$$

has been prepared in 17% yield through the dehydration of cyanuric tricarboxylic amide with P_2O_5. It crystallizes in monoclinic prisms melting at 119° and boiling at 262° under 771 mm. It is readily decomposed by atmospheric moisture giving cyanuric acid. It is not acted upon by chlorine[138].

Polymerization of Cyanogen

Cyanogen vapors may be kept indefinitely at room temperature in the absence of water and light[90]. The compound begins to polymerize to *paracyanogen*, (CN)x, at 220° under a pressure of 300 atmospheres[91], and at 310° at atmospheric pressure without decomposition. Paracyanogen depolymerizes completely above 860° under atmospheric pressure[92]. Potassium cyanide and potassium carbonate accelerate the polymerization of cyanogen; glass and quartz have slight catalytic action[93]. Paracyanogen is obtained readily by the electrolysis of a solution of potassium cyanide[94]. The compound is not soluble in organic solvents.

Polymerization of Cyanamide

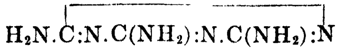
Cyanamide, $H_2N.CN$, condenses in slightly alkaline aqueous solution to a dimer, *dicyanodiamide*[95], $H_2N.C(:NH).NH.CN$.

Polymerization takes place quantitatively in alkaline solutions up to pH 10. The velocity of polymerization is a function of the hydrogen ion concentration, reaching a maximum at pH 9.8 and decreasing rapidly below and above this point[96].

In the presence of 2–4% ammonia, the conversion of cyanamide to dicyanodiamide proceeds rapidly and is nearly quantitative. In the temperature range 98–104°, conversion is complete within about 25 minutes[97]. Acids also cause the polymerization of cyanamide. The compound appears to be quite stable in neutral aqueous or alcoholic solution[98]. Cyanamide also undergoes polymerization when heated alone in the absence of any solvent[99].

Alkyl and aryl cyanamides polymerize to trialkyl- or triaryl substituted *iso*melamines upon heating them alone or in solution in alcohol or water. Methyl-, ethyl-, *iso*amyl-, phenyl-, *p*-tolyl- and benzyl-substituted *iso*melamines have been prepared in this manner[100].

Melamine,



$$\mathrm{H_2N.C{:}N.C(NH_2){:}N.C(NH_2){:}N}$$

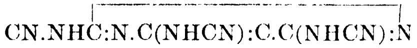
the trimer of cyanamide, may be obtained by heating cyanamide or dicyanodiamide at 120–125° in a closed vessel in an inert atmosphere, under 50–100 pounds pressure[101]. Melamine forms also when a mixture of dicyanodiamide and ammonium chloride is heated to 180°, guanidine, its hydrochloride, and some insoluble decomposition product forming simultaneously[102]. Another method of preparation of melamine from dicyanodiamide is to heat the latter in an autoclave with liquid or gaseous ammonia. A pure product may be obtained by this method[103].

The commercial process for the preparation of melamine as developed in Germany is described as follows:

A slurry is made consisting of 4,200 pounds of dicyanodiamide and 3,600 pounds of *iso*butyl alcohol and is homogenized in a wet grinding mill. This is pumped during 4–5 hours into a 1,000-gallon autoclave previously charged with 176 pounds of anhydrous ammonia and heated to 180–185°. The temperature is maintained between 180 and 190° during the pumping period, the operating pressure being 30–40 atm. After all the dicyanodiamide suspension has been added, the temperature is maintained at 185° for two hours. The mass is then cooled to 25–30° and filtered. The cake is dried by distillation of the solvent, the distillate and the filtrate being combined to be used in the preparation of the next batch. The crude melamine is stirred in dilute sodium hydroxide solution, filtered and washed. The wet cake contains approximately 3,630 pounds of melamine, the yield being, therefore, 87% of theory.

N-Substituted melamines may be prepared by heating mixtures of melamine and a mineral acid salt of a primary or secondary aliphatic or aromatic amines at 150–200°[104], or mixtures of melamine and the free amines in a closed vessel at 250–280°.

Sodium dicyanamide, $NaN(CN)_2$, is converted to a trimer, tricyanomelamine,



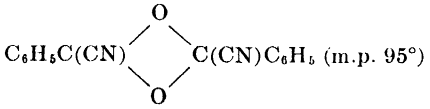
$$CN.NHC{:}N.C(NHCN){:}C.C(NHCN){:}N$$

when heated to a dark red heat.

Sodium dicyanamide is prepared by the action of cyanogen bromide on an aqueous solution of sodium cyanamide. Dicyanamide, $HN(CN)_2$, is one of the strongest of organic acids, though it is not stable and polymerizes rapidly[106].

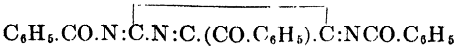
Polymerization of Miscellaneous Other Nitriles

Cases are known of the polymerization of nitriles, in which reactive groups other than the nitrile group play a role. Thus, *benzoyl cyanide*, C_6H_5COCN, forms a dimer,



(m.p. 95°)

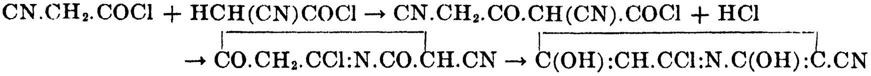
when heated in ethereal solution in the presence of sodium for 48 hours[107]. Benzoyl cyanide also forms a trimer[108]; the formula



$$C_6H_5.CO.N{:}C.N{:}C.(CO.C_6H_5).C{:}NCO.C_6H_5$$

has been assigned to this compound by Diels and Stein[109]. A dimolecular *acetyl cyanide* has also been prepared from acetyl cyanide by the action of metallic sodium or solid alkali metal hydroxides[110].

Cyanoacetyl chloride is unstable at room temperature even in the pure state and changes on standing to 6-chloro-2,4-dihydroxynicotinonitrile, probably via the following steps:



$$CN.CH_2.COCl + HCH(CN)COCl \rightarrow CN.CH_2.CO.CH(CN).COCl + HCl$$
$$\rightarrow CO.CH_2.CCl{:}N.CO.CH.CN \rightarrow C(OH){:}CH.CCl{:}N.C(OH){:}C.CN$$

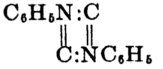
At higher temperatures, the transformation takes place with explosive violence and with evolution of a considerable volume of fumes[111].

Cyanoacetyl chloride may be obtained in 99.5% yield by the action of phosphorous pentachloride on cyanoacetic acid[112]. The compound may be prepared more economically by passing a current of chlorine into a solution of cyanacetic acid and phosphorous trichloride in ethyl ether. It may be distilled almost without decomposition in a high vacuum, boiling at 59° under 0.05 mm[113].

Weddige[114] obtained a polymer of *cyanoethyl formate* by saturating an ethereal solution of the compound with hydrochloric acid and heating in a sealed tube at 100° for a few hours. The polymer melted at 165°.

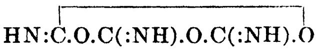
Polymerization of *Iso*cyanides, Cyanates, Thiocyanates, etc.

Ethyl isocyanide, $C_2H_5.N{:}C$, polymerizes to a trimer, $C_9H_{15}N_3$, on heating to 100–160°; the trimer decomposes to propionitrile when heated above 160°, decomposition being complete at 240°[115]. *Phenyl isocyanide* readily polymerizes to a dimer, possibly[139]



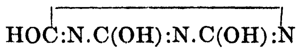
$$\begin{array}{l} C_6H_5N{:}C \\ \quad C{:}NC_6H_5 \end{array}$$

Vapors of *cyanic acid* polymerize to cyamelide,



$$HN{:}C.O.C({:}NH).O.C({:}NH).O$$

at temperatures below 150°, and to cyanuric acid,



$$HOC{:}N.C(OH){:}N.C(OH){:}N$$

at higher temperatures[116]. Liquid cyanic acid polymerizes at 0° within one hour to a solid consisting principally of cyamelide and a small proportion of cyanuric acid[117].

Werner and Fearon[118] showed that the proportion of cyamelide and cyanuric acid formed varies with the temperature. The amounts of cyamelide and cyanuric acid formed at temperatures between 0 and 20° were as follows:

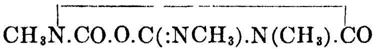
Temperature, °C	*Cyamelide, %*	*Cyanuric Acid, %*
0	59.3	40.7
5	58.6	41.4
10	57.3	42.7
20	42.9	57.1

According to Klason[119], cyanic acid polymerizes to cyanuric acid in ethereal solution and in the presence of hydrogen chloride.

Ethyl isocyanate polymerizes readily to ethyl cyanurate[120].

Heated to 50 to 60° in an organic solvent, *thiocyanic acid* forms a dimer, cyanamidodithiocarbonic acid, CN.NH.CS.SH. Below 40°, the acid decomposes in organic solvents other than alcohol to hydrocyanic acid and xanthydric acid. In ethereal solution, the acid remains unchanged in the cold for several days[121].

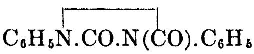
Methylisocyanate polymerizes to a trimer, trimethyl *iso*cyanurate, m.p. 175°[122,123]. An abnormal polymerization takes place in the presence of triethylphosphine, and 3,5-dimethyl-2-methylimino-4,6-diketo-1,3,5-oxdiazin,



$$CH_3N.CO.O.C(:NCH_3).N(CH_3).CO$$ (m.p. 114°)

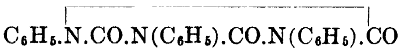
forms; simultaneously a small quantity of trimethyl *iso*cyanurate forms[122,124].

In contact with small quantities of triethylphosphine, *phenyl isocyanate* condenses to a dimer, diphenyl di*iso*cyanate[125],



$$C_6H_5N.CO.N(CO).C_6H_5$$

The condensation also takes place on boiling a pyridine solution of phenyl *iso*cyanate[126]. A trimer, triphenyl *iso*cyanurate,



$$C_6H_5.N.CO.N(C_6H_5).CO.N(C_6H_5).CO$$

forms when phenyl *iso*cyanate is heated to 100° with potassium acetate[127]. Tolyl *iso*cyanate polymerizes similarly.

Thiocyanic acid dissolves in water at 0° without decomposition, but it polymerizes rapidly at higher temperatures to a yellow polymer.

When to a concentrated aqueous solution of a thiocyanate, moderately concentrated sulfuric or hydrochloric acid is added a yellow, sparingly soluble, voluminous solid is precipitated consisting principally of dithiocyanic acid, $H_2C_2N_2S_2$.

Methyl thiocyanate polymerizes at 190° in the presence of a trace of hydrogen chloride to trimethyl thiocyanurate;* *ethyl thiocyanate* also polymerizes to the trithiocyanuric ester under the same conditions[128]. *Isoamyl thiocyanate* polymerizes to a small extent at 190° in the presence of a trace of a mineral acid.

Methyl isothiocyanate polymerizes to a trimer on heating with potassium acetate[129].

A trimer of *fulminic acid*, cyan*iso*nitrosoacethydroxamic acid, CN.C(:NOH).-C(NOH).OH, forms on adding ammonia to a solution of formyl chloride oxime[130], HC(:NOH)Cl. In ethereal solution, fulminic acid rapidly polymerizes to *iso*cyanuric acid.

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Chapter 18

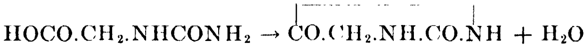
Reactions of Cyanates, Thiocyanates and *Iso*cyanides

REACTION OF CYANATES AND THIOCYANATES

Reaction with Amines

Amine salts of cyanic and thiocyanic acids, which are obtained by the direct combination of amines with the free acids or by the interaction of amine hydrochlorides with alkali salts of the acids, are transformed on heating to ureas and thioureas, respectively. The transformation of ammonium cyanate to urea was the earliest example of the direct synthesis of a compound supposed to be a product of the living organism only. The transformation is quite general, though it takes place with varying degrees of ease, depending on the nature of the amine.

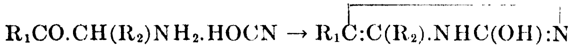
The cyanates of amino acids may also be transformed to ureas; thus, carboxymethylurea, $HOCO.CH_2.NH.CONH_2$, may be obtained from glycine cyanate. The α-carboxylic ureas are readily transformed to hydantoins by loss of a molecule of water[1]:



$$HOCO.CH_2.NHCONH_2 \rightarrow CO.CH_2.NH.CO.NH + H_2O$$

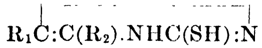
Thiohydantoins may be obtained in a similar manner from α-amino acid thiocyanates[2].

Cyanates of α-aminoketones are transformed to imidazolone derivatives by internal condensation:



$$R_1CO.CH(R_2)NH_2.HOCN \rightarrow R_1C{:}C(R_2).NHC(OH){:}N$$

Thiocyanates of α-aminoketones undergo the same type of transformation, forming mercaptoimidazole derivatives[3]:

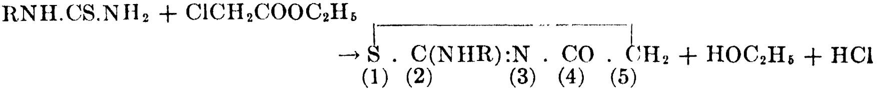


$$R_1C{:}C(R_2).NHC(SH){:}N$$

o-Tolylurea has been prepared from *o*-toluidine and potassium cyanate in aqueous or dilute acetic acid solution[4]. *p*-Tolylurea has been obtained by adding a solution of potassium cyanate to a hot aqueous solution of *p*-toluidine sulfate or hydrochloride[5]. 2,4-Dimethylphenylurea has been obtained by adding an aqueous solution of *m*-xylidine to one of potassium cyanate[6]. 2-Chlorophenylurea, $Cl.C_6H_4NH.CONH_2$, has been made by adding a solution of potassium cyanate to the aqueous solution of an equivalent quantity of *o*-chloraniline hydrochloride[7]. *Benzylurea* is formed on heating, for a short time, benzylamine hydrochloride and potassium cyanate in aqueous solution[8]. *o*-Methylbenzylurea, $CH_3C_6H_4.CH_2.NH.CONH_2$, has been prepared from *o*-methylbenzylamine and potassium cyanate in aqueous solution[9]. *α-Naphthylurea* has been obtained by the interaction of α-naphthylamine and cyanic acid in ether solution[10] and also from an aqueous solution of α-naphthylamine hydrochloride and potassium cyanate[11]. *β-Naphthylurea* has also been prepared by the latter method[6,11]. *β-Phenylethylurea*, $C_6H_5.CH_2.CH_2NH.CONH_2$, forms on heating a solution of β-phenylethylamine hydrochloride and potassium cyanate. N-Methyl-N-β-phenylethylurea is similarly obtained from methyl-β-phenylethylamine hydrochloride[12]. Phenylthiourea forms on heating aniline thiocyanate on a water-bath for two to three hours[13]. *m*-Tolylthiourea is obtained by passing a current of ammonia into an ethereal solution of *m*-tolyl *iso*thiocyanate[14]. β-Phenylethylthiourea has been prepared from β-phenylethylamine hydrochloride and potassium thiocyanate[15]. α-Naphthylthiourea forms on heating on a water-bath an aqueous solution of α-naphthylamine hydrochloride and ammonium thiocyanate[16]. β-Naphthylthiourea has been obtained from β-naphthylamine and potassium thiocyanate, on prolonged heating on a water-bath[17].

Diphenylamine hydrochloride, heated with ammonium thiocyanate at 110 to 120° for five hours in chlorobenzol solution, gives N,N-diphenylthiourea. Analogous disubstituted thioureas may be obtained by the same method from phenyl-α-naphthylamine, *p*-tolyl-β-naphthylamine, *p*-methoxyphenyl-β-naphthylamine, and di-*p*-hydroxyphenylamine[18].

Heated with chloroethylacetate, thioureas form thiazolidones:



$$RNH.CS.NH_2 + ClCH_2COOC_2H_5 \rightarrow \underset{(1)}{S} . \underset{(2)}{C}(NHR):\underset{(3)}{N} . \underset{(4)}{CO} . \underset{(5)}{CH_2} + HOC_2H_5 + HCl$$

Roberts and Dains[19] have obtained the following by this method: 2-*p*-phenoxyphenylamino-4-thiazolidone, m.p. 183.5°; 2-*p*-phenoxyphenylimino-3-phenoxyphenyl-4-thiazolidone, m.p. 131°; 2-*o*-phenoxyphenylamino-4- thiazolidone, m.p. 147.5°.

The three isomeric phenylenediureas have been obtained from the corresponding cyanates. The transformation of the cyanates takes place rapidly even at room temperature. Phenylenedithioureas have also been obtained from the dithiocyanates by heating these latter[20].

Thiocyanates of aminobenzyl cyanide and aminophenylacetic methyl ester have been transformed to the corresponding ureas[21]: $H_2NCONH.C_6H_4.CH_2CN$, $H_2NCO.NH.C_6H_4.CH_2COOCH_3$. The thiocyanate of *p*-phenetidine hydrochloride undergoes transformation to *p-phenetol carbamide* (Dulcin), $C_2H_5OC_6H_4.NHCONH_2$.

Potassium cyanate reacts with salts of *hydroxylamine* forming hydroxyurea, *iso*hydroxyurea, hydroxybiuret, urea and a potassium compound of unknown structure[22]: $KC_4H_9O_6N_6$. With the neutral hydrochloride of *sym.* dimethylhydrazine, potassium thiocyanate forms 1,2-dimethyl semicarbazide[23], $H_2NCON(CH_3).NH.CH_3$.

Potassium cyanate reacts with free *cyanamide* in aqueous solution forming monocyanurea, $CN.NH.CONH_2$, or

$$HN:C.NH.CO.NH$$

The maximum yield in solution of optimum acidity is not over 50% of the theoretical.

Reaction with Halogen Acids and Other Inorganic Acids

Chlorothiocarbamide, H_2NCSCl, has been obtained by the action of hydrochloric acid on free thiocyanic acid. Thiourethanes have been prepared from this compound[28].

Hydrogen chloride reacting with slightly moist potassium thiocyanate gives a white, snow-like compound which Klason[29] considered to be chlorothio carbamide, $H_2NCS.Cl$.

Hydrochloric acid of 1.2 density decomposes potassium thiocyanate, giving the compound $C_2H_4N_2S$. The reaction is one of hydrolysis:

$$5HSCN + 5H_2O \rightarrow C_2H_4N_2S_4 + CO_2 + 3NH_3 + CH_2O_2 + COS$$

Hydrogen bromide, reacting with ethyl thiocyanate forms ethyl thioformamide dibromide, $C_2H_5SCBr_2NH_2$. This compound is readily decomposed with water[30].

Ethyl thiocyanate reacts with hydrogen sulfide forming dithiourethane[31], $H_2NCS.SC_2H_5$. *Iso*propyldithiourethane has been obtained by the same reaction from *iso*propyl thiocyanate[32].

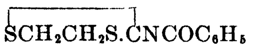
Hydrazoic acid reacts with cyanic acid forming carbamic azide[33], HOC-(:NH).N_3. *Iso*cyanic and *iso*thiocyanic esters react in a similar manner[34].

Reaction with Organic Acids

Normal thiocyanates react with thioacetic acid and other thio-acids forming, in general, acylated thiocarbamic esters[35]:

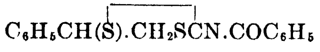
$$RSCN + HS.COCH_3 \rightarrow RSCS.NH.COCH_3$$

Methylene dithiocyanate, $CH_2(SCN)_2$, reacting with *thiobenzoic acid*, gives, in addition to the benzoylated dithiocarbamic ester, $CH_2(SCSNHCOC_6H_5)_2$, the compounds $CH_2(SCSNH_2)_2$ and $C_6H_5COS.CH_2SCSNHCOC_6H_5$. *Ethylene dithiocyanate*, CNS.CH_2CH_2S.CN, gives, with *thiobenzoic acid*, the two compounds $H_2NSCSCH_2CH_2CS.SNH_2$ and



$$SCH_2CH_2S.CNCOC_6H_5$$

Phenylethylene dithiocyanate, $C_6H_5CH(SCN).CH_2SCN$, gives the compound[36]



$$C_6H_5CH(S).CH_2SCN.COC_6H_5$$

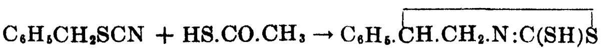
Phenyl thiocyanate and certain other thiocyanates react with thio-acids, forming esters of the thio-acid:

$$C_6H_5SCN + HSCO.C_6H_5 \rightarrow C_6H_5S.CO.C_6H_5 + HNCS$$

Thiocyanic acid gives the amide of the oxy-acid[36]:

$$HSCN + HS.COC_6H_5 \rightarrow H_2N.CO.C_6H_5 + CS_2$$

Benzyl thiocyanate forms 2-thio-4-phenylthiazoline (m.p. 168°) with *thioacetic acid*[37]:

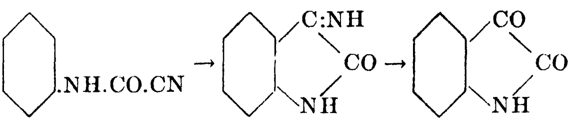


$$C_6H_5CH_2SCN + HS.CO.CH_3 \rightarrow C_6H_5.CH.CH_2.N{:}C(SH)S$$

Carbon dioxide combines with *methyl isocyanate* in alcohol solution and in the presence of triethyl phosphine forming 3,5-dimethyl-2,4,6-triketo-1,3,5-oxdiazine[38]:

$$CH_3N.CO.N(CH_3).CO.OCO \text{ (m.p. 255–258°)}$$

Hydrocyanic acid reacts with *methyl isocyanate* in the presece of triethyl phosphine forming methylaminoformyl cyanide[39], $CH_3NH.COCN$. This reaction takes place also with other *iso*cyanates. Cyanoformylarylamides condense in the presence of aluminum chloride to cyclic imides from which isatins are obtained by hydrolysis[40]:



Hydrocyanic acid reacts with *phenyl isocyanate,* in the presence of a trace of alkali, forming cyanoformanilide; the latter then condenses with a second molecule of phenyl *iso*cyanate to 1,3-diphenylparabanic acid-4-imide:

$$C_6H_5NCO + HCN \rightarrow C_6H_5NH.COCN$$

$$C_6H_5NCO + C_6H_5NHCOCN \rightarrow C_6H_5N.CON(C_6H_5).CO.C{:}NH$$

Further reaction with a third molecule of *iso*cyanate leads to the formation of a phenylureidoparabanic acid:

$$C_6H_5N.CON(C_6H_5).CO.C{:}NH + C_6H_5NCO$$
$$\rightarrow C_6H_5N.CON(C_6H_5)CO.C{:}NCO.NH.C_6H_5$$

A certain amount of cyanoformyldiphenylurea, $CNCO.N(C_6H_5)CONH.C_6H_5$, also forms[41].

Aromatic *iso*thiocyanates react with potassium cyanide in alcoholic solution, forming derivatives of thioxamic nitriles[42]:

$$ArN{:}CS + KCN \rightarrow ArNK.CS.CN$$

Reaction with Halogens

In the presence of water and in the cold, chlorine converts aliphatic or substituted aliphatic thiocyanates to chlorosulfones:

$$RSCN + 3Cl_2 + 2H_2O \rightarrow RSO_2Cl + Cl.CN + 4HCl$$

The reaction proceeds less readily with phenyl thiocyanate. The chlorination of benzyl thiocyanate in 80% acetic acid results in the formation principally of benzyl chloride[43]. Dry chlorine reacts with methyl thiocyanate according to the equation[44]:

$$3CH_3.SCN + 11Cl_2 \rightarrow Cl_3(CN)_3 + 2CSCl_4 + SCCl_2 + 9HCl$$

Thiocyanogen iodide, ISCN, forms by the reaction of iodine with silver thiocyanate[45].

Chlorine, passed over heated alkaline or alkaline-earth thiocyanates, reacts to form polymers of thiocyanogen and loose combinations of these with the metallic chlorides. The coloring matter *Canarin* has been obtained from these products[46]. Canarin may be prepared in better yield through the interaction of chlorine with a concentrated solution of alkaline or alkaline-earth thiocyanates. A large proportion of *pseudothiocyanogen* also results in this reaction. Other oxidizing agents such as nitric acid hydrogen peroxide, persulfates, etc., may be employed instead of chlorine[47]. Canarin may be obtained in a pure form as follows:

To a solution of one part of potassium thiocyanate in two parts of water are added ⅕ of the total required quantity (about ½ part) of potassium chlorate and one part of concentrated hydrochloric acid. When the vigorous reaction which ensues subsides to some extent, the reaction vessel is immersed in cold water and the remaining potassium chlorate is added gradually, together with one part of hydrochloric acid. The temperature is maintained at 80° during the reaction. The precipitated solid is filtered, washed and is dissolved in twenty times its own weight of 5% aqueous sodium hydroxide solution, by the application of heat. The solution is cooled to 40° and is diluted with an equal weight of alcohol, whereby the sodium compound of Canarin precipitates out. Canarin is liberated from this by treatment with a mineral acid. The process of solution in alkali, precipitation with alcohol, etc., is repeated, and the resulting product is thoroughly washed and dried. It is then extracted carefully with warm carbon disulfide, treated with boiling alcohol and filtered and dried. The yield is quite low, usually less than 4% on the basis of the thiocyanate employed. The empirical formula of the material thus purified is $H_6C_8N_8S_7O$; the sodium salt is represented by the formula $Na_2H_4C_8N_8S_7O$.

Canarin is a reddish brown amorphous powder possessing a metallic luster. It is insoluble in water, alcohol, benzene and other organic solvents. It dissolves in aqueous solutions of alkalies. Its solutions in alkalies dye vegetable fibers a bright yellow, the colors being quite fast.

Many investigators have confused *pseudo*thiocyanogen with Canarin. There is some doubt as to the exact nature of *psuedo*thiocyanogen. The yield and composition of this product vary to some extent according to the method of preparation and according to the conditions. Hydrogen and oxygen are component parts of the molecule and the empirical formula $H_4C_4N_4S_4O$ has been ascribed to the compound. It would appear that Canarin results through the hydrolysis of a true thiocyanogen compound (CNS)x, under the action of an alkali:

$$(CNS)_{12} + 6H_2O \rightarrow C_8H_6N_8S_7O + H_4C_3N_4S_2O + COS + H_2S_2O_3$$

When a current of chlorine is led into a solution of potassium selenocyanate, a red precipitate forms. Kype and Neger[48] believed this to be perselenocyanogen. On continued passage of chlorine, the red compound gives a yellow product, which these authors considered to be perselenocyanic acid. Vernenill[49] showed that the red product has the empirical formula C_2NSe_3.

Reaction of Alkali Thiocyanates with Organic Halogen Compounds

Alkali or alkaline-earth thiocyanates react with compounds containing active chlorine to give thiocyano derivatives. Thus, thiocyanates have been prepared through the interaction of sodium thiocyanate and compounds containing the group $>C{=}CH.CH_2Cl$. From allyl chloride, allyl thiocyanate is obtained:

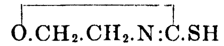
$$CH_2{=}CH.CH_2Cl + NaSCN \rightarrow CH_2{=}CH.CH_2SCN + NaCl$$

1-Chlorobutene-2, 1-chloro-2-methyl-butene-2 and 1,3-dichloropropene-2 react similarly.

It is sufficient, as a rule, to heat the aqueous solution of the thiocyanate with the organic chloride under a reflux condenser. A good yield of allyl thiocyanate may only be obtained, however, by heating the chloride and thiocyanate under pressure[50].

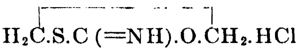
Ethylene dibromide, reacting with potassium thiocyanate, forms ethylene dithiocyanate, $CNS.CH_2CH_2SCN$, and ethylene bromothiocyanate, $BrCH_2CH_2SCN$, in low yield[51].

Potassium thiocyanate reacts with ethylene chlorohydrin, forming β-hydroxyethyl thiocyanate, $HOCH_2.CH_2.SCN$. The compound also forms by the interaction of thiocyanic acid and ethylene oxide[225]. This compound may be converted by internal rearrangement to mercaptoöxazoline,



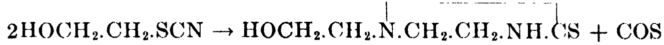
$$O.CH_2.CH_2.N{:}C.SH$$

Hydrochloric acid converts β-hydroxyethyl thiocyanate to a compound of the probable formula[225]



$$H_2C.S.C(=NH).O.CH_2.HCl$$ (m.p. 121.5°)

Ethoxy-1-mercaptodihydroimidazole forms through the condensation of two molecules of compound[52]:



$$2HOCH_2.CH_2.SCN \rightarrow HOCH_2.CH_2.N.CH_2.CH_2.NH.CS + COS$$

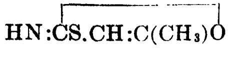
Potassium thiocyanate reacts with chloromethyl ether, $ClCH_2OCH_3$, in petroleum ether solution on boiling under reflux for 60 hours, forming thiocyanomethyl ether, CH_3OCH_2SCN, $b.p._{10} = 33.5\text{–}35.5°$, in 87% yield[53].

Ammonium thiocyanate reacts with chloroacetone to form thiopropimin thiocyanate in 30% yield[54]:

$$CH_3COCH_2Cl + 2NH_4SCN \rightarrow CNS.CH_2.C(CH_3){:}NH.HSCN + NH_4Cl + H_2O$$

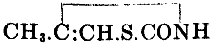
Barium thiocyanate, reacting with chloracetone in alcohol solution, forms thiocyanoacetone[55], $CNS.CH_2.COCH_3$. Aqueous solutions of alkaline thiocyanates also give this compound[56].

Thiocyanoacetone cyclizes slowly in aqueous solution. Cyclization is accelerated by hydrochloric acid, and is complete within about 1 hour in warm 2-normal hydrochloric acid. Tschernaic believed the cyclic compound has the structure:



$$HN{:}CS.CH{:}C(CH_3)O$$

Hantzsch proposed the formula:

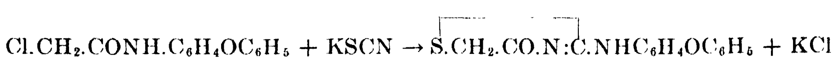


$$CH_3.C{:}CH.S.CONH$$

and offered proof as to its correctness. It appears probable that the rhodamin type forms as an unstable intermediate[57].

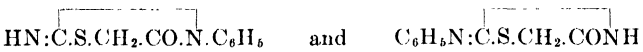
Potassium thiocyanate reacting with chloracetic acid gives *iso*thiocyanoacetic acid[58], $S:C:N.CH_2COOH$.

Potassium thiocyanate reacts with chloroacetamides to form thiazolidones[19]:



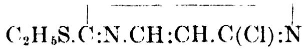
$$Cl.CH_2.CONH.C_6H_4OC_6H_5 + KSCN \rightarrow S.CH_2.CO.N:C.NHC_6H_4OC_6H_5 + KCl$$

With chloracetanile, three compounds are formed[59]: $NCS.CH_2CONHC_6H_5$,



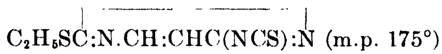
$$HN:C.S.CH_2.CO.N.C_6H_5 \quad \text{and} \quad C_6H_5N:C.S.CH_2.CONH$$

Potassium thiocyanate may form with halogenated pyrimidines either *iso*thiocyanates or thiourethanes. Ethylthio-2-chloro-6-pyrimidine,



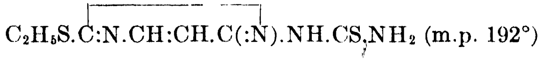
$$C_2H_5S.C:N.CH:CH.C(Cl):N$$

gives ethylthio-2-*iso*thiocyano-6-pyrimidine,



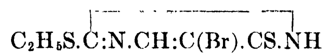
$$C_2H_5SC:N.CH:CHC(NCS):N \text{ (m.p. } 175°)$$

Methyl-5-chloro-6-ethylthio-2-pyrimidine gives the thiourea,



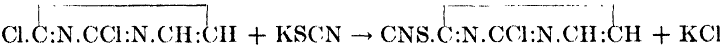
$$C_2H_5S.C:N.CH:CH.C(:N).NH.CS.NH_2 \text{ (m.p. } 192°)$$

Ethylthio-2-bromo-5-chloro-6-pyrimidine gives ethylthio-2-bromo-5-thio-6-pryimidine,



$$C_2H_5S.C:N.CH:C(Br).CS.NH$$

yellow plates, m.p. 195°, as well as a 6-amino derivative[60]. Potassium thiocyanate reacts at 100° with 2,6-dichloropyrimidine in alcoholic solution, forming 2-chloro-6-thiocyanopyrimidine, m.p. 283–284°, in 40% yield[61]:



$$Cl.C:N.CCl:N.CH:CH + KSCN \rightarrow CNS.C:N.CCl:N.CH:CH + KCl$$

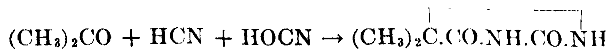
6-Chloro-2-ethylthiopurimidine, 6-chloro-2-ethylthio-5-methylpyrimidine and 6-chloro-2-ethylthio-5-bromopyrimidine react with potassium cyanate to form first the corresponding normal thiocyanates which are converted on long heating to *iso*thiocyanates[226].

Sulfur monochloride, S_2Cl_2, reacts with metallic thiocyanates at moderately high temperature to form sulfur thiocyanate[62], $S.(SCN)_2$. In carbon disulfide and at low temperature, $S_2(SCN)_2$ forms[63].

Ethyl β-selenocyanopropionate, $CH_3.CH(SeCN).COOC_2H_5$, is obtained by heating ethyl β-chloropropionate with potassium selenocyanate in alcoholic solution[227].

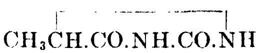
Miscellaneous Reactions

The reaction of cyanic acid with acetone and hydrocyanic acid leads to the formation of acetonylurea[64]:



$$(CH_3)_2CO + HCN + HOCN \rightarrow (CH_3)_2C.CO.NH.CO.NH$$

Aldehyde ammonia, reacting with cyanic and hydrocyanic acids, forms the corresponding aldehyde compound[65]:



$$CH_3CH.CO.NH.CO.NH$$

Potassium cyanate reacts at 0° with a mixture of hydroxylamine hydrochloride and an aromatic aldehyde in aqueous solution giving nitrones[66]:

$$RCHO + KCNO + H_2NOH.HCl \rightarrow RCH{:}NO.CONH_2 + H_2O + KCl$$

Certain nitrones are reduced with potassium cyanide to ureids[67]:

$$RCH{:}NO.CONH_2 + KCN \rightarrow RCH{:}NCONH_2 + KCNO$$

Cyanic acid adds compounds, such as alcohols, ammonia, amines, halogen or *pseudo*halogen acids, as well as oxyacids, the negative portion of the compound combining with carbon, the positive portion with nitrogen. With sulfuric acid, the compound first formed is $HO.CO.NH.SO_3H$; in ether solution, a second molecule of cyanic acid combines with this, giving $HOCO.NH.SO_2NHCOOH$, which finally changes to $H_2N.SO_2NH.COOH$.

The zinc salt of terephthalic acid reacts with lead thiocyanate, forming terephthalic nitrile (*Van Epps and Reid reaction*).

Sodium ethoxide reacts with phenyl thiocyanate to form the sodium salt of thiophenol and ethyl *iso*cyanate[228] C_2H_5NCO.

REACTIONS OF *ISO*CYANATES AND *ISO*THIOCYANATES

Reaction with Amines

*Iso*cyanates react with amino compounds, forming substituted ureas according to the equation:

$$R.N{:}CO + H_2NR' \rightarrow RNH.CO.NH.R'$$

Thus, *methyl isocyanate* reacts with *ammonia* in ether solution forming methylurea[68]. With *methylamine*, N,N'-dimethylurea[69], and with *aniline*, N-methyl-N'-phenylurea[68] are formed. Cyanamide condensing with methyl *iso*cyanate in the presence of triethylphosphine gives bis-(methylcarbaminyl)-cyanamide[229], $(CH_3NHCO)_2N.CN$. Ethylurea has been prepared from aqueous *ammonia* and *ethyl isocyanate*[70]. N,N'-Diethylurea and N,N,N'-triethylurea have been prepared similarly from *ethyl-* and *diethylamines* and ethyl *iso*cyanate[71].

Phenylurea has been obtained by the reaction of *phenyl isocyanate* and *ammonia*[72]. N-Methyl-N'-phenylurea is formed when gaseous *methylamine* is led into a solution of phenyl *iso*cyanate in anhydrous ether[73]. N,N-Diethyl-N'-phenylurea is similarly formed from *diethylamine* and phenyl *iso*cyanate[74]. Carbanilide is obtained in the same manner from *aniline*[72], and N-methyl-N,N'-diphenylurea from *methylaniline* and phenyl *iso*cyanate. *Ethylaniline* and *diphenylamine* react similarly[75].

Phenyl *iso*cyanate reacts with *methylenedianiline*, $CH_2(NHC_6H_5)_2$, forming methylene-bis-[N,N′-diphenylurea][77]: $[C_6H_5.NH.CON(C_6H_5)]_2CH_2$. With *toluenediamine*, toluene-bis-[N,N′-diphenylurea]; and with *m-phenylenediamine*, *m*-phenylene-bis-[N,N′-diphenylurea] are formed[78]. With *anthranilic acid*, reaction proceeds vigorously with evolution of carbon dioxide and formation of N,N′-diphenyl-N-[2-aminobenzoyl] urea[79]: $H_2N.C_6H_4.CON(C_6H_5).CONH.C_6H_5$.

Aminoacid salts react with phenyl *iso*cyanate, forming ureidoacid salts:

$$H_2N.R.COONa + C_6H_5NCO \rightarrow C_6H_5NH.CO.NH.R.COONa$$

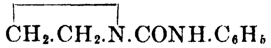
The free acids, as a rule, do not react readily[76,80].

Paal and Ganser[81] prepared the following:

	M.P. °C
o-Phenylureidocinnamic acid, $C_6H_5NHCONHC_6H_4CH{:}CHCOOH$	236
o-Phenylureidodihydrocinnamic acid, $C_6H_5NHCONH.C_6H_4CH_2.CH_2$-COOH	168
o-Phenylureidodibromocinnamic acid, $C_6H_5NH.CO.NH.C_6H_4CHBrCHBr$-COOH	227
Also *m*- and *p*-phenylureido homologs of these, and *p*-Phenylureidobenzosulfonic acid, $C_6H_5NH.CO.HNC_6H_4SO_3H(p)$	dec. at 270
α,β-Phenylmethylureidoacetic acid, $C_6H_5NH.CO.NH(CH_3).CH_2.COOH$	102

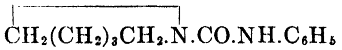
Heated with *3-aminobenzoic acid* in a sealed tube at 100°, phenyl *iso*cyanate reacts to form 3-[ω-phenylureido]-benzoic acid[82,83].

Cyclic amines also give substituted ureas with phenyl *iso*cyanate. Thus, *ethyleneimin* reacts in the cold forming N-ethylene-N′-phenylurea[84]:



$$CH_2.CH_2.N.CONH.C_6H_5$$

Piperidine gives N-anilinoformylpiperidine[74]:



$$CH_2(CH_2)_3CH_2.N.CO.NH.C_6H_5$$

Phenyl *iso*cyanate reacts with a concentrated aqueous solution of *hydroxylamine* in excess forming N-anilinoformylhydroxylamine[85], $C_6H_5NH.CONHOH$. With *methylhydroxylamine*, N-hydroxy-N-methyl-N′-phenylurea[86], $C_6H_5.NH.$-$CON(CH_3)OH$ is obtained. Ethylhydroxylamine reacts similarly. Phenylhydroxylamine gives N-hydroxy-N,N′-diphenylurea[87]. O-Benzylhydroxylamine, reacting with one molecular equivalent of phenyl *iso*cyanate, forms O-benzylanilinoformylhydroxylamine, $C_6H_5NH.CONH.OCH_2C_6H_5$; with two molecular equivalents of phenyl *iso*cyanate, it gives O-benzyl-N,N′-dianilinoformyldhydroxylamine[88], $(C_6H_5NHCO)_2N.OCH_2C_6H_5$.

Methylhydrazine in ether solution reacts with phenyl *iso*cyanate, forming 2-methyl-4-phenylsemicarbazide[89], $C_6H_5NH.CON(CH_3).NH_2$. With unsymmetrical dimethylhydrazine, 1,1-dimethyl-4-phenylsemicarbazide is obtained[90]; and with *sym.* dimethylhydrazine, N,N′-dimethylhydrazine-N,N′-dicarboxylic dianilide is formed[23]. Ethylhydrazine gives 2-ethyl-4-phenylsemicarbazide[91].

Phenyl hydrazine reacts with phenyl *iso*cyanate in the absence of a solvent or in solution in alcohol or benzene, formining exclusively 1,4-diphenylsemicarbazide; in alcoholic acetic acid, there is formed in addition a small quantity of 2,4-diphenylsemicarbazide[92].

p-Nitrophenylhydrazine reacts very rapidly with *iso*cyanates; other substituted hydrazines react slowly. *p*-Nitrophenyl-α-methylhydrazine requires long heating on a water-bath, while 3,4-dinitrophenyl-α-methylhydrazine does not react appreciably with methyl- and phenyl *iso*cyanates on heating at 100° for ten hours[232].

Methylnitramine, $CH_3NH.NO_2$, reacts with phenyl *iso*cyanate, forming N-nitro-N-methyl-N′-phenylurea[93]. *Dimethyltriazine* forms dimethyltriazinecarboxylic anilide[94], $C_6H_5.NH.CO.N(CH_3)N{:}N.CH_3$.

Diazoaminobenzene, $C_6H_5N{:}N.NH.C_6H_5$, reacts with phenyl *iso*cyanate in ligroin solution, forming the compound $C_6H_5.NH.CO.N(C_6H_5).N{:}N.C_6H_5$. Other diazoamino compounds react in a similar manner[95].

Amides and *amidines* also react with phenyl *iso*cyanate, giving substituted ureas[82]. Acetamide forms N-phenyl-N-acetylurea; acetamidine gives N,N′-dianilinoformylacetamidine[96]: $C_6H_5.NH.CO.N{:}C(CH_3).NH.CONH.C_6H_5$. Other amidines react similarly. *Benzamidoxime* gives ω-phenylureidobenzoxime[97], $C_6H_5NH.CO.NH.C(C_6H_5){:}NOH$.

Benzanilide reacts with phenyl *iso*cyanate, forming benzenyldiphenylamidine, m.p., 144°[78]:

$$C_6H_5CO.NH.C_6H_5 + CO{:}NC_6H_5 \rightarrow C_6H_5C({:}NC_6H_5).NH.C_6H_5 + CO_2$$

Phenyl *iso*cyanate reacts with *guanidine thiocyanate* in alcoholic solution in the presence of sodium ethoxide forming N,N′-dianilinoformylguanidine[98], $(C_6H_5NHCONH)_2C{:}NH$, m.p. 174–175°.

*Iso*cyanates react with *ureas* forming biurets. Thus, ω, ω'-diphenylbiuret, $C_6H_5NH.CONH.CONH.C_6H_5$, forms on heating a mixture of phenyl *iso*cyanate and phenylurea at 120°[99]. Phenyl*iso*cyanate and methylurea give ω-phenyl-ω'-methylbiuret, $C_6H_5NH.CONH.CONH.CH_3$, m.p. 132–133°, and a little ω-phenyl-ω-methylbiuret, $C_6H_5NH.CON(CH_3).CONH_2$, m.p. 183°. An ω'-nitroso derivative may be prepared from the former, but not from the latter. ω-Phenyl-ω'-methylbiuret also forms as a result of the reaction of methyl*iso*cyanate with phenylurea, together with other as yet unidentified products[249].

*Iso*cyanates, RNCO, reacting with monosodium cyanamide give the sodium salt of cyanoureas of the type RNHCONH.CN. Methyl *iso*cyanate in cold ethereal solution reacts with cyanamide in the presence of triethylphosphine to form bis(methylcarbaminyl)cyanamide, $(CH_3NHCO)_2N.CN$, in 80% yield[229].

Additional amino compounds, from which the corresponding substituted ureas have been prepared by reaction with phenyl *iso*cyanate, are given below, together with references to the original articles:

Ethylenediamine	Loewy, and Neuberg, *Z. phys. Chem.*, **43**, 355 (1903).
Aminoethylalcohol	Gault, H., *Bull. soc. chim.*, (4) **3**, 370 (1908).
Aminoacetonitrile	Klages, A., *J. prakt. Chem.*, (2) **65**, 190 (1902).
α-Aminopropionitrile	Delépine, M., *Bull. soc. chim.*, (3) **29**, 1193 (1903).
Nitroaniline	Leuckart, R., *ibid.*, (2) **41**, 322 (1890).
Phenylenediamines	Lellemann, E. and Würthner, E., *Ann.*, **228**, 220 (1885).

Diaminodiphenylmethane, $CH_2(C_6H_4NH_2)_2$	Senier, A. and Goodwin, W., *J. Chem. Soc.*, **81,** 283 (1902); Senier, A. and Shepheard, F. G., *ibid.*, **95,** 496 (1909).
Formanilide	Schmidt, O., *Ber.*, **36,** 2480 (1903).
Acetanilide	Busch, M., Blume, G. and Pungs, E., *J. prakt. Chem.*, (2) **79,** 517, 538 (1909).

Many substituted ureas have been prepared through the reaction of amines with 4-diphenyl *iso*cyanate[230] and with *p*-nitrophenyl *iso*cyanate[231]. The latter reacts slowly with diphenylamine, gives an impure product with pyrrole and does not react with indole.

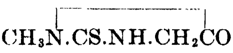
High molecular polymers have been obtained through the interaction of diisocyanates with di- and polyamino compounds[256].

Isothiocyanates react with amino compounds in the same manner as *isocyanates*, forming thioureas:

$$RNCS \rightarrow H_2NR' \rightarrow RNH.CSNHR'$$

Methylthiourea is obtained from *methyl isothiocyanate* and an alcoholic solution of *ammonia*[100,101]. With *methylamine* in alcoholic solution, N,N′-dimethylthiourea is obtained[100]. The reaction is similar with dimethylamine[102] and with aniline[103].

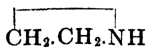
Methyl *iso*thiocyanate, added gradually to a solution of one molecular equivalent of *hydrazine hydrate* in alcohol cooled in ice, reacts to form thiocarbamic hydrazide[104]. With *methylhydrazine* in alcoholic or ethereal solution, dimethyl thiosemicarbazide, $CH_3NH.CS.N(CH_3).NH_2$, is obtained[105,106]. Similarly, methylphenylthiosemicarbazide forms from *phenylhydrazine* and methyl *iso*thiocyanate[106,107]. With *hydroxylamine* in ether, N′-hydroxy-N-methylthiourea results[108]. Methyl *iso*thiocyanate reacts with *sodium cyanamide* in alcoholic solution, forming N-methyl-N′-cyanothiourea[109]. In concentrated alcoholic caustic solution, methyl *iso*thiocyanate reacts with *glycine*, forming methylthiohydantoin[110]:



$$CH_3N.CS.NH.CH_2CO$$

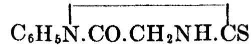
Ethyl isothiocyanate gives with *ammonia*, N-ethylthiourea, and with ethylamine N,N′-diethylthiourea[111]. With *diethylamine*, it forms N,N,N′-triethylthiourea[112]. Ethyl *iso*thiocyanate reacts with the ethyl ester of *aminocrotonic acid*, forming the compound[113] $CH_3C(:NH).CH(COOC_2H_5).CS.NH.C_2H_5$. With *sodium cyanamide*, the sodium salt of N-ethyl-N′-cyanothiourea is obtained. Other *iso*thiocyanates react in a similar manner[109]. Alkylated derivatives have been prepared from the sodium compounds of cyanothioureas obtained from various *iso*thiocyanates and alkyl iodides[114]. *Hydroxylamine* reacts with ethyl *iso*thiocyanates, forming N′-hydroxy-N-ethyl thiourea; with *ethyl hydroxylamine*, N′-hydroxy-N,N′-diethylthiourea forms[115].

Phenyl isothiocyanate forms phenylthiourea by direct reaction with *ammonia*[116]; with *ethylamine*, N-ethyl-N′-phenylthiourea is obtained[117]; with *dimethylamine*, N,N-dimethyl-N′-phenylthiourea forms[118]. *Ethylene diamine*, in cold alcoholic solution, gives ethylene-bis-(ω-phenylthiourea). *Trimethylenediamine* reacts in a similar manner[119]. *Ethyleneimine*,



$$CH_2.CH_2.NH$$

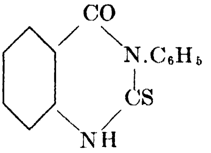
reacts with phenyl *iso*thiocyanate, forming ethyleneimine-N-thiocarbanilide[120]. *Ethanolamine* forms N-(β-hydroxy ethyl)-N′-phenylthiourea[121]. *Glycine* gives 3-phenyl-2-thiohydantoin[122],



$$C_6H_5N.CO.CH_2NH.CS$$

Aniline reacts with *phenyl isothiocyanate* on gentle warming to form thiocarbanilide[116,123].

N-phenyl-N′-*m*-tolythiourea forms on evaporating down an alcoholic solution of phenyl *iso*thiocyanate and *m-toluidine* or of *m*-tolyl *iso*thiocyanate and *aniline*[102]. *Diphenylamine* reacts after several days' heating at 250° and then only to form a small amount of triphenylthiourea[124]. *o-Phenylenediamine* in alcohol solution, reacting with one equivalent of phenyl *iso*thiocyanate, forms N-phenyl-N′-(2-aminophenyl)-thiourea; with two molecular equivalents, *o*-phenylene-bis-(ω-phenylthiourea) forms. *Meta-* and *para-phenylenediamines* react similarly[125]. Phenyl *iso*thiocyanate gives with *methyl anthranilate*, keto-N-phenyl-3-thio-4-tetrahydroquinazoline[126]:



which sublimes at 160–170°.

Halophenylphenyl *iso*thiocyanates which may be prepared through the interaction of a halophenylamine and phenyl *iso*thiocyanate, are hydrolyzed by dilute sulfuric acid to halophenyl *iso*thiocyanate and aniline. This offers a means for the preparation of halogenated phenyl *iso*thiocyanates. *p*-Chlorophenyl- 2,4-dichlorophenyl- and 2,4-dibromophenyl *iso*thiocyanates have been made by this method[251].

Hydroxylamine reacts with phenyl *iso*thiocyanate, forming N′-hydroxy-N-phenylthiourea. Hydroxylamine reacts in a similar manner with other aromatic *iso*thiocyanates[127]. Aromatic hydroxythioureas are comparatively stable, in contrast with the aliphatic analogs, which, because of their lack of stability, have never been isolated in the pure form.

*Iso*thiocyanates react with primary *alkyl hydrazines* to form thiosemicarbazides, the group, —CS.NHR, replacing the α-hydrogen in the hydrazine:

$$RNH.NH_2 + CSNR' \rightarrow RN(NH_2)CSNH.R'$$

p-Substituted phenylhydrazines also form α-compounds, but *o*- and *m*-substituted compounds form the β-compound, R.NH.NH.CS.NHR′. *Phenylhydrazine* combines with *iso*thiocyanates to form the labile *trans*-thiosemicarbazides; these, upon heating or on boiling with a trace of hydrochloric acid in alcoholic solution, change to the stable *cis*-isomers[128].

Hydrazine hydrate in alcoholic solution, reacting in the cold with one equivalent of phenyl *iso*thiocyanate, forms 4-phenylthiosemicarbazide[129]. On heating on a water-bath one molecular equivalent of hydrazine sulfate and two molecular equivalents of phenyl *iso*thiocyanate in alcoholic solution, in the presence of sodium carbonate, hydrazine-N,N′-bis-thiocarbanilide forms[130]. *Methylhydrazine* reacts with phenyl *iso*thiocyanate to form 2-methyl-4-phenylthiosemicarbazide[131]. *Phenylhydrazine* in alcoholic solution, reacting in the cold with phenyl *iso*thiocyanate, forms 2,4-diphenylthiosemicarbazide[132]. If external cooling is not applied, and the reaction mixture is allowed to warm spontaneously, the product formed is 1,4-diphenylthiosemicarbazide[133]. *Benzhydrazide* reacts with phenyl *iso*thiocyanate in alcoholic solution, forming 4-phenyl-1-benzoylthiosemicarbazide[134], $C_6H_5.NH.CSNH.NH.COC_6H_5$. *Benzamidine* gives N-anilinothioformylbenzamidine[135]. *Benzamidoxime* gives benzoic (ω-phenylthioureid)-oxime[136]. $C_6H_5NH.-CS.NH.C(:NOH).C_6H_5$.

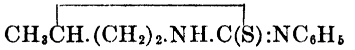
Two parts of *guanidine carbonate*, heated at 100° with three parts of phenyl *iso*thiocyanate and some alcohol, form N-phenyl-N′-guanylthiourea, $C_6H_5.NH.-CS.NH.C(NH).NH_2$, and thiocarbanilic-O-ethyl ester[137], $C_6H_5NHCSOC_2H_5$. Phenyl *iso*thiocyanate reacts with *sym. diphenylguanidine* in benzol solution in the cold, forming N-phenyl-N′-(diphenylguanyl)-thiourea[138].

Phenyl *iso*thiocyanate reacts with *diacetonitrile* at 140–150°, forming β-[anilidoformylimino]-butyronitrile:

$$C_6H_5NCS + HN{:}C(CH_3).CH_2CN \rightarrow C_6H_5NH.CS.N{:}C(CH_3)CH_2CN$$

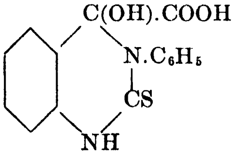
A similar reaction takes place with benzoacetodinitrile[139].

Phenyl *iso*thiocyanate reacts with *γ-chlorobutylamine* to form the heterocyclic compound[140]:



$$CH_3CH.(CH_2)_2.NH.C(S){:}NC_6H_5$$

Isatin reacts with phenyl *iso*thiocyanate to form 2-thio-3-phenyl-4-hydroxy-1,2,3,4-tetrahydroquinazoline-4-carboxylic acid



(m.p. 159–160°)

Phenyl *iso*cyanate gives 2-keto-3-phenyl-4-hydroxy-1,2,3,4-tetrahydroquinazoline-4-carboxylic acid, m.p. 173–174°[252].

Reaction with Alcohols

*Iso*cyanates react with alcohols forming urethanes, *i.e.* carbamic esters, according to the general equation:

$$RNCO + HOR' \rightarrow RNH.CO.OR'$$

Thus, N-ethylcarbamic ethyl ester results from the reaction of *ethyl alcohol* with ethyl *iso*cyanate[141]. Under the action of sodium ethoxide, ethyl *iso*cyanate is converted largely to the triethyl ester of *iso*cyanuric acid[142].

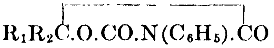
Phenyl *iso*cyanate combines with *methyl alcohol* with evolution of heat, forming the methyl ester of carbanilic acid, $C_6H_5NH.COOCH_3$, m.p. 47°.

When heated with concentrated sulfuric acid and then treated with a large volume of bromine water, this compound is converted to N-[2,4-dibromophenyl]-methyl urethane.

Other aliphatic alcohols[143] including secondary and tertiary alcohols[144] also form carbanilic acid esters with phenyl *iso*cyanate. Bloch prepared *n*-octyl-, *sec.*-octyl-, undecyl-, hexadecyl- and myricylphenylurethanes by this method[145]. *Ethylene glycol* gives with phenyl *iso*cyanate the dicarbanilic acid ester of ethylene glycol[146]. Glycerol gives glycerol tris-(phenyl carbamate)[25], $C_3H_5(OCONH.C_6H_5)_3$.

Lambling[147] prepared phenylurethanes from phenyl *iso*cyanate and the *ethyl esters* of *glycolic, lactic, β-hydroxybutyric, trichlorolactic, mandelic* acids; also from phenyl isocyanate and *chloral cyanohydrin* and *mandelonitrile.*

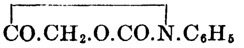
Phenyl *iso*cyanate forms phenylurethanes of the type $C_6H_5.NH.CO.O.C(R_1,R_2).COOC_2H_5$, with esters of *α-hydroxy acids*, $R_1R_2C(OH).COOH$. When these compounds are saponified to the corresponding acids and heated to 100° they form the internal anhydrides:



$$R_1R_2C.O.CO.N(C_6H_5).CO$$

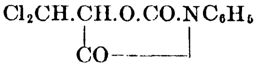
Lambling[148] has prepared compounds of this type, in which R_1 and R_2 were the following: H,H; H,CH_3; H,C_6H_5; $H,CH_2.CH_3$; $H,CH_2.CH_2.CH_3$; $H,CH(CH_3)_2$; C_2H_5,C_2H_5; C_6H_5,C_6H_5. The compound, o-$C_6H_4(COOC_2H_5)OCO.NH.C_6H_5$, has also been prepared by this author.

The free *α*-hydroxy acids form compounds of the type $C_6H_5HNCO.O.C(R_1,R_2).CO.NHC_6H_5$. The glycolic acid derivative, heated on the free flame, gives the internal anhydride:



$$CO.CH_2.O.CO.N.C_6H_5$$

Trichlorolactic acid forms an anhydride directly[149]



$$\begin{array}{l}Cl_2CH.CH.O.CO.NC_6H_5\\ \quad\quad\;\; CO\end{array}$$

Phenylurethanes of *sugars* may be prepared by the following method:

A mixture of the sugar with phenyl *iso*cyanate in 25% excess is diluted with three times its volume of anhydrous pyridine and the whole is boiled for a few minutes. The pyridine is then evaporated off and the residue is extracted first with alcohol then with water. The urethane is obtained as an amorphous or microcrystalline powder which is very slightly soluble in the usual solvents. It is decomposed on heating. The sugar urethanes do not reduce Fehling's solution.

Phenylurethanes were prepared by Maquenne and Godwin[150] by this method from *l-xylose, d-glucose, d-galactose, lactose, trehalose, melezitose, mannite, dulcite* and *persite.*

Phenyl *iso*cyanate also reacts with *phenol*, forming carbanilic acid phenyl ester, $C_6H_5NH.COOC_6H_5$, m.p. 126°. This compound decomposes, when distilled, into phenol and phenyl *iso*cyanate[151]. Carbamates of this type have also been prepared through the interaction of phenyl *iso*cyanate with resorcinol, hydroquinone, pyrogallol, methyl salicylate, *α*-naphthol, eugenol and phenylphenol[27]. A small amount of anhydrous aluminum chloride greatly accelerates the reaction[152]. Sodium also has a catalytic action[153]. *4-Nitrophenol* reacts with phenyl *iso*cyanate at water-bath temperature, forming the 4-nitrophenyl ester of carbanilic acid[154]; *2-nitrophenol* reacts only to a slight extent, even on long heating at 150–170° in a sealed tube[155]. *Triphenylcarbinol* does not form a carbanilic ester with phenyl *iso*cyanate[156].

Pyrocatechin reacts with phenyl *iso*cyanate on heating at 100° for ten to sixteen hours in a sealed tube forming a dicarbanilic ester, $(C_6H_5NHCOO)_2C_6H_4$, m.p. 165°. *Resorcinol* and *hydroquinone* react similarly[157]. Resorcinol reacts more readily in ether solution and in the presence of a small quantity of metallic sodium[158]. *Pyrogallol* forms a tricarbanilic ester; phlorglucinol reacts even at room temperature though slowly[159]. The reaction is accelerated by traces of alkali[160].

p-Nitrophenylcarbamic esters have been prepared through the interaction of *p*-nitrophenyl *iso*cyanate[231] and 4-diphenyl *iso*cyanate[230] with various alcohols and phenols.

Condensation products of di- or poly*iso*cyano compounds with polyhydroxy compounds of high molecular weight have been produced in Germany (Ingamids) and serves as *plastics*. They possess many valuable properties. The principal *iso*cyanates used are toluylene di*iso*cyanate (Desmodur T) and hexamethylene di*iso*cyanate (Desmodur H). These are condensed with 1,4-butanedoil and with adipic esters (Desmophens) prepared from trimethylolpropane or a mixture of this with 1,4-butanediol.

The reaction of *isothiocyanates* with alcohols is similar to that of *iso*cyanates, the reaction products being thiocarbanilic esters:

$$R.N:CS + HOR' \rightarrow RNH.CS.OR'$$

Thus, *ethyl alcohol* reacts with *ethyl isothiocyanate* at 110° forming N-ethylthiocarbamic ethyl ester[161]. The saturated aliphatic alcohols react in this manner with phenyl *iso*thiocyanate[162]. Phenol, hydroquinone, pyrogallol and aromatic alcohols, such as benzyl alcohol do not react with *iso*thiocyanates[163].

Thiocarbanilide has been obtained through the reaction of phenyl *iso*thiocyanate with glycerine[164]. *m*-Tolylthiourethane has been made by heating tolyl*iso*thiocyanate with absolute alcohol at 130°[165].

Acyl *iso*thiocyanates, RCONCS, react with alcohols to form acylthion carbomates, RCONHCSOR'[26].

Reaction with Mercaptans

The reaction of mercaptans with *iso*cyanates is similar to that of alcohols:

$$RNCO + HSR' \rightarrow RNH.CO.SR'$$

Ethyl mercaptan, heated with *phenyl isocyanate* in a sealed tube at 100°, forms thiocarbanilic S-ethyl ester[166]. *Phenyl mercaptan*, heated with phenyl *iso*cyanate in a sealed tube at 100° for 15 hours gives thiocarbanilic S-phenyl ester[167]: $C_6H_5NH.COSC_6H_5$.

Phenyl isothiocyanate reacts with *mercaptans* to form dithiocarbanilic acid esters. Thus, ethyl dithiocarbanilate[168], $C_6H_5NH.CS.SC_2H_5$, is obtained from *ethyl mercaptan* and dithiocarbanilic benzyl ester from *benzyl mercaptan*[169].

Thioglycolic acid condenses with phenyl *iso*thiocyanate to phenylrhodanic acid:

$$C_6H_5NCS + HS.CH_2COOH \rightarrow C_6H_5\overline{N.CS.S.CH_2.C}O + H_2O$$

Similarly methylphenylrhodanic acid,

$$C_6H_5\overline{N.CS.SCH(CH_3).C}O$$

forms from phenyl *iso*thiocyanate and *thiolactic acid*[170].

Heated with *hydrogen sulfide* to 40°, ethyl *iso*thiocyanate reacts forming carbon disulfide and N,N'-diethylthiourea[171].

Reaction with Halogen Acids

*Iso*cyanates react with hydrochloric acid, forming substituted chloroformamides[172]:

$$RN{:}CO + HCl \rightarrow RNH.CO.Cl$$

Chloroformanilide has been prepared by this method from phenyl *iso*cyanate[173]. Bromoformanilide has also been prepared similarly by the interaction of hydrobromic acid and phenyl *iso*cyanate[174].

Phenylcarbamyl fluoride, $C_6H_5NH.CO.F$, m.p. 32°, has been obtained in quantitative yield through the interaction of hydrogen fluoride with phenyl *iso*cyanate in the cold. The compound is non-lachrymatory and fairly stable, though it evolves hydrogen fluoride when heated at 100°. Carbamyl fluorides have also been prepared from *p*-tolyl-, *p*-nitrophenyl-, hexadecyl-, hexamethylene bis- and *m*-phenylene bis- *iso*cyanates. Phenyl *iso*thiocyanate does not yield a stable product with hydrogen fluoride[268].

Reaction with Organic Acids

Organic acids react at moderate temperature with *phenyl isocyanate*, forming the anhydride of the acid and diphenylurea:

$$2R.COOH + 2CONC_6H_5 \rightarrow (RCO)_2O + CO(NHC_6H_5)_2 + CO_2$$

At higher temperatures the anhydride reacts with the diphenylurea formed giving the anilide of the acid:

$$(RCO)_2O + CO(NHC_6H_5)_2 \rightarrow 2RCONH.C_6H_5 + CO_2$$

With dibasic acids, $R(COOH)_2$, the phenylimide, $R(CO)_2NC_6H_5$, may form in the second stage[175].

Heated to 170° with *malonic acid*, phenyl *iso*cyanate reacts to form malonic dianilide, $CH_2(CONHC_6H_5)_2$. *Sebacic* and *azelaic dianilides* have been obtained similarly[176]. Mixed with *cyanoacetic acid*, phenyl *iso*cyanate reacts in the cold, forming cyanoacetanilide[177]:

$$CN.CH_2COOH + OC{:}NC_6H_5 \rightarrow CN.CH_2CONH.C_6H_5 + CO_2$$

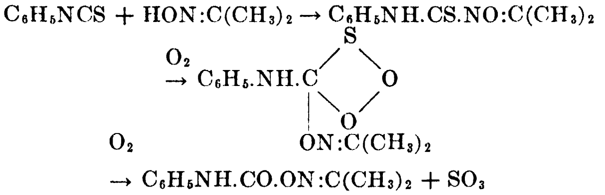
Similar compounds are obtained from α-cyanopropionic, α-cyanobutyric and α-cyanovaleric acids[178]. *Succinic acid* forms phenylsuccinimide when heated with phenyl *iso*cyanate or phenyl *iso*thiocyanate[176]. *Phthalic acid*, heated to 200° with two molecules of phenyl *iso*cyanate, forms phthalanil. Reaction takes place at 150–160° with *isophthalic acid;* terephthalic acid does not react even at 210°[179].

*Iso*thiocyanates react readily with *oximes* forming unstable resinous compounds which are difficult to purify. *Aldoximes* give addition products which decompose immediately into a nitrile, a thiocarbanilide and carbon sulfoxide, the probable course of the reaction being as follows[180]:

$$C_6H_5NCS + HON{:}CH.C_6H_5 \rightarrow C_6H_5NH.CS.ON{:}CH.C_6H_5 \rightarrow C_6H_5CN + C_6H_5NH.CSOH$$

$$2C_6H_5NHCSOH \rightarrow (C_6H_5NH)_2CS + COS + H_2O$$

Ketoximes also give addition products which change to compounds devoid of sulfur. The probable course of the reaction is exemplified by the following:

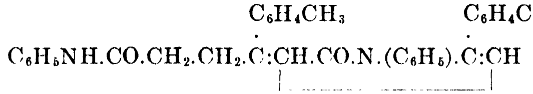


$$C_6H_5NCS + HON{:}C(CH_3)_2 \rightarrow C_6H_5NH.CS.NO{:}C(CH_3)_2$$

$$\xrightarrow{O_2} C_6H_5NH.CO.ON{:}C(CH_3)_2 + SO_3$$

Phenyl *iso*cyanate reacts with *sodio ethyl formylacetate* giving sodio formylmalonic ethyl ester anilide[181]. Acetylmalonic ethyl ester anilide is formed with *ethyl acetoacetate* at water-bath temperature, or on long standing at ordinary temperature[182].

Tolylbutanoic acid, $CH_3C_6H_5.COCH_2CH_2COOH$, heated gradually to 210° with phenyl *iso*cyanate forms the compound[183]:



$$C_6H_5NH.CO.CH_2.CH_2.\overset{C_6H_4CH_3}{C}{:}CH.CO.N.(C_6H_5).\overset{C_6H_4CH_3}{C}{:}CH$$

Phenyl *iso*cyanate reacting with *diethyl malonate* in the presence of a trace of alkali forms methanetricarboxylic diethyl ester anilide[184], $C_6H_5NHCO.CH(COOC_2H_5)_2$; with *sodio ethyl cyanoacetate* the sodium compound of cyanomalonic ethyl ester anilide forms[185].

Sodio diethyl malonate, reacting with phenyl *iso*thiocyanate gives the compound $C_6H_5N{:}C(SNa).CH(COOC_2H_5)_2$; this is transformed under the action of hydrochloric acid to[186] $C_6H_5NH.CS.CH(COOC_2H_5)_2$. Similar compounds are obtained from allyl *iso*thiocyanate and sodio diethyl malonate[187].

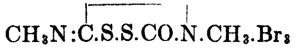
*Iso*thiocyanates react with *thiobenzoic acid*, forming N-substituted benzamides[188]:

$$RNCS + HSCOC_6H_5 \rightarrow RNH.CO.C_6H_5 + CS_2$$

Reaction with Halogens

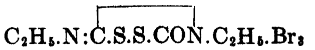
Phenyl *iso*cyanate reacts with chlorine in chloroform solution forming the highly unstable dichloride $C_6H_5OCNCl_2$. The reaction with bromine is similar[189].

Bromine reacting with methyl *iso*thiocyanate in alcoholic chloroform solution forms methyliminomethyldisulfazolidone tribromide[190]:



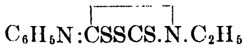
$$CH_3N{:}C.S.S.CO.N.CH_3.Br_3$$

Similarly, ethyl *iso*thiocyanate, reacting with bromine in cold alcoholic solution, forms 2-ethylimino-1-ethyl-3,4-disulfazolidone-5-tribromide[191]:



$$C_2H_5.N{:}C.S.S.CON.C_2H_5.Br_3$$

In ligroin solution, the bromine addition product of 2-ethylimino-5-thio-1-ethyl-3,4-disulfazolidine,



$$C_6H_5N{:}CSSCS.N.C_2H_5$$

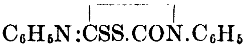
is obtained in low yield[192]. This compound decomposes to ethylamine, carbon dioxide and hydrogen sulfide when heated with water at 200° or with concentrated hydrochloric acid at 100°[193].

*Iso*thiocyanates in chloroform solution react with chlorine to form *iso*cyano dichlorides[194], $RN{:}CCl_2$. Thus, with phenyl *iso*thiocyanate in solution in an equal volume of chloroform, phenyl *iso*cyanodichloride forms:

$$C_6H_5NCS + 2Cl_2 \rightarrow C_6H_5NCCl_2 + SCl_2$$

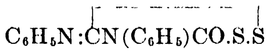
*Iso*cyanodichlorides react with amines to form guanidines; thus, triphenylguanidine, $C_6H_5NC(NHC_6H_5)_2$, is obtained from phenyl *iso*cyanodichloride and aniline[195].

The reaction of chlorine with phenyl *iso*thiocyanate in chloroform solution also leads to the formation of a chlorinated product which is changed upon treatment with water or alcohol to phenylphenyliminodisulfazolidone[196]:



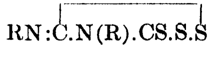
$$C_6H_5N{:}CSS.CON.C_6H_5$$

Reacting with bromine in chloroform containing a little water, phenyl *iso*thiocyanate gives bis-(phenylthiocarbimide)-oxide[197]:



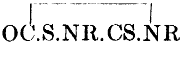
$$C_6H_5N{:}CN(C_6H_5)CO.S.S$$

It would appear that the primary reaction products of an *iso*thiocyanate and bromine in an indifferent solvent are the compounds: $(RNCS)_2Br_2$ and $(RNCS)_2SBr_x$, the former yielding upon reaction with water an oxide, $(RNCS)_2O$, and the latter a sulfide, $(RNCS)_2S$. The *iso*thiocyanoöxide forms when the reaction between the *iso*thiocyanate and bromine is carried out in the presence of a little water. Freund[198] believed that these compounds have the following structures:



$$RN{:}C.N(R).CS.S.S$$

and

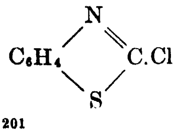


$$OC.S.NR.CS.NR$$

Phenyl *iso*thiocyanate, heated five to six hours with phosphorus pentachloride at 160° in a sealed tube, gives *iso*cyanophenyl chloride[199]:

$$C_6H_5NCS + PCl_5 \rightarrow C_6H_5.NCCl_2 + PSCl_3$$

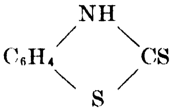
2-Chlorobenzothiazole,



also results from the reaction[200,201].

Reaction with Sulfur

Phenyl *iso*thiocyanate heated with sulfur at 250–260° in a sealed tube forms 2-thionbenzothiazoline[202],



Reaction with Hydrocarbons in Presence of Aluminum Chloride

Phenyl *iso*cyanate reacts with aromatic hydrocarbons in the presence of anhydrous aluminum chloride forming anilides:

$$C_6H_6 + OC{:}N.C_6H_5 \rightarrow C_6H_5.CO.NH.C_6H_5$$

Phenylcarbamic chloride, $C_6H_5NH.CO.Cl$, appears to be formed first, the hydrogen chloride required for its formation resulting from the partial decomposition of aluminum chloride.

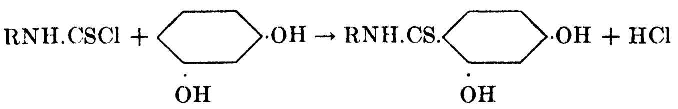
Leuckart[203] prepared compounds of this type from benzene, toluene, xylenes, *pseudo*cuminol, diphenyl, naphthalene, alkyl ethers of phenol, *p*-cresol, α-naphthol and β-naphthol. The group, —$CONHC_6H_5$, enters the *ortho*-position with respect to CH_3 in toluene; and the 4-position in *ortho*- and *meta*-xylene. Strongly negative elements or groups attached to the aromatic nucleus generally hinder the reaction, though halogenated phenol ethers react very readily.

Phenyl *iso*thiocyanate reacts with aromatic hydrocarbons or phenol ethers in presence of aluminum chloride, giving thiocarbanilides[204]:

$$C_6H_5NCS + C_6H_6 \rightarrow C_6H_5NH.CS.C_6H_5$$
$$C_6H_5NCS + C_6H_5OCH_3 \rightarrow C_6H_5NH.CS.C_6H_4OCH_3$$

As in the case of *iso*cyanates a carbamic chloride, RNHCS.Cl, forms first which then reacts with the hydrocarbon. Karrer and Weiss[205] prepared thioacid amides by this reaction from *iso*thiocyanates and polyhydric phenols, such as phlorglucinol, pyrogallol, and resorcinol:

$$RNCS + HCl \rightarrow RNH.CS.Cl$$



With phenol reaction proceeds at room temperature, *p*-hydroxythiobenzanilide being obtained in 80% yield. *m*-Cresol gives 2-methyl-4-hydroxythiobenzanilide; *p*-cresol gives 2-hydroxy-5-methylthiobenzanilide; phlorglucinol forms 2,4,6-trihydroxythiobenzanilide. The anilide of 1-hydroxy-2-thionaphthoic acid is obtained in 80% yield from α-naphthol; β-naphthol forms the anilide of 2-hydroxy-1-thionaphthoic acid in poor yield[233].

Miscellaneous Reactions

Methyl *iso*cyanate results from the reaction of ***diazomethane*** and cyanic acid in ether solution[206]. Methyl *iso*cyanate condenses with diazomethane in presence of triethyl phosphine, forming methylcarbamic acid methyl ester[39]: CH_3-$NHCOOCH_3$, b.p. 61°.

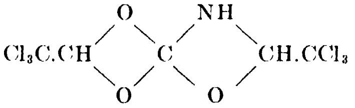
Phenyl *iso*thiocyanate reacts with diazomethane to form phenylaminothiobiazole[207],

$$C_6H_5.NH.C{:}CH.N{:}N.S$$

Cyanic acid reacting with cold *acetaldehyde* forms trigenic acid[208]:

$$NH.CONH.CH(CH_3).NH.CO$$

Anhydrous cyanic acid reacts with *chloral* to form a glassy mass, from which the compound,



has been isolated[209].

Cyanic acid combines with thiocyanic acid in ether solution, forming carbamic thiocyanate[210], $H_2N.CO.SCN$, m.p. 69°, dec. at 105°.

Potassium cyanate reacts with a boiling solution of *epichlorhydrin* in water forming a monochloraminopropylaminocarbamic ester:

$$ClCH_2.CH.CH_2NH.CO.O$$

or its isomer[211]:

$$ClCH_2CH.CH_2O.CONH$$

Cyanic acid gives an addition product.

Ammonium thiocyanate reacts with *acetylacetone*, forming a purple colored compound melting at 177°, soluble in pyridine, and boiling alcohol[212].

Ethyl thiocyanate combines with *trimethylamine*, forming ethyltrimethylammonium thiocyanate, m.p. 131–132°. The benzyl analog melts at 117–118°. Methyl selenocyanate gives with trimethylamine, tetramethyl ammonium selenocyanate, m.p. 267–268° (dec.)[213].

Phenyl *iso*thiocyanate reacts with *chloroacetic acid* in warm alcoholic or ethereal solution forming 3-phenyl-2,4-dioxothiazolidine ("phenyl mustard oil glycolide")[214],

$$C_6H_5.NCOSCH_2CO$$

Alkyl *iso*thiocyanates, R.N:CS, in which R is one of the groups: ethyl, propyl, butyl or amyl, react in the cold with *N-Alkyl Schiff bases* forming dithioketocyanidines[215]:

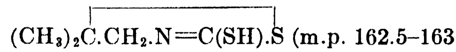
$$R_1CH{:}NR_2 + 2RNCS \rightarrow R_1CH.NR.CS.NR.CSNR_2$$

*Iso*cyanates react in a similar manner:

$$R_1CH{:}NR_2 + 2RN{:}CO \rightarrow R_1CH.NR.CO.NR.CONR_2$$

Phenyl *iso*cyanate reacts less readily, reaction taking place at a good rate only at about 150°[216]. *N-Aryl Schiff bases* do not give these addition compounds.

Methallyl *iso*thiocyanate, $CH_2{:}C(CH_3).CH_2.N{:}C{:}S$, is converted by concentrated sulfuric acid to dimethyl-5,5-mercapto-2-thiazoline[234],



$$(CH_3)_2C.CH_2.N{=}C(SH).S$$ (m.p. 162.5–163°)

Allyl thiocyanate heated with a concentrated solution of potassium hydrosulfite, $KHSO_3$, gives the compound $CH_2{:}CH.CH_2NH.CS.SO_3K$, which decomposes on heating with sulfuric acid and with dilute sodium carbonate solution[253].

Nitration of *o*-tolyl thiocyanate leads to the formation of 5-nitro-*o*-tolyl thiocyanate, m.p. 117.5–118.5°, a small quantity of the 4-nitro isomer, melting at 70–71° forming at the same time. Phenyl selenocyanate gives principally 4-nitrophenyl selenocyanate, m.p. 141°, and a small quantity of the 2-nitro-isomer[235].

REACTIONS OF THIOCYANOGEN

Thiocyanogn, CNS.SCN, has the characteristics of a *pseudo*halogen, and like halogens adds at multiple bonds of certain unsaturated compounds forming dithiocyano compounds. By this reaction have been prepared, for example, ethylene dithiocyanate, m.p. 90–90.5°, styrene dithiocyanate, m.p. 102.5–103°, cyclohexene dithiocyanate, m.p. 58–58.5°, 3-methylcyclohexene dithiocyanate, m.p. 69.5–70°. Liquid products incapable of purification are obtained from some unsaturated compounds[217].

The thiocyanogen required for the reaction may be prepared by a variety of methods. A simple and effective procedure is to cause bromine to react with lead thiocyanate in suspension in anhydrous ether. To illustrate, a suspension of 6.6 grams of lead thiocyanate in 50 cc. of absolute ether is shaken with 3.2 grams of bromine until the color of bromine disappears. The filtered solution is then ready for use[257].

Thiocyanogen may also be prepared through the oxidation of thiocyanic acid in non-aqueous media with manganese dioxide, or better still, with lead tetraacetate[258]. Rapid reaction and good yields are obtained when thiocyanogen is generated in the reaction mixture. The procedure consists in dissolving the compound to be thiocyanated in 96% acetic acid containing sodium thiocyanate in solution and adding an equivalent of bromine also dissolved in 96% acetic acid. For example, aniline may be effectively thiocyanated by proceeding as follows: To a solution of 3.7 grams of aniline in 7 cc of 96% acetic acid is added one of 8.5 grams of sodium thiocyanate in 45 cc of the same acid. The mixture is cooled in ice and agitated, while a solution of 1.5 grams of bromine in 14 cc of acetic acid is added drop by drop[259].

The thiocyanogen may also be generated through the electrolysis of an aqueous solution of ammonium thiocyanate at 0° at a current density of 0.2–0.3 amp./sq. cm. The thiocyanogen thus produced is utilized directly in the reaction with the compound to be thiocyanated. Thiocyano compounds have been obtained by this method from phenol, cresols, *o*- and *m*-toluidine, ethyl aniline, 8-hydroxyquinoline, thymol, diethylphenol and carvacrol[222]. Thiocyano compounds have also been prepared by this method from *p*-toluidine, anisidine, *p*-phenetidine and ethyl *p*-aminobenzoate, and the products converted to 2-aminobenzothiazoles[260].

Finally, thiocyanogen may be generated through the spontaneous decomposition of cupric thiocyanate in the presence of the compound to be thiocyanated, the cupric thiocyanate being reduced to cuprous thiocyanate in the process[261]:

$$2Cu(SCN)_2 + RH \rightarrow RSCN + HSCN + 2CuSCN$$
$$2Cu(SCN)_2 + RCH{=}CHR' \rightarrow RCH(SCN).CH(SCN)R' + 2CuSCN$$

The reactivity of thiocyanogen is greatly influenced by solvents; thus, reaction proceeds vigorously when nitromethane is used as a solvent. Reactivity is also enhanced by light rays and by certain catalysts such as ferric thiocyanate.

Kaufmann and Liepe[262] investigated the stability of solutions of thiocyanogen and found that in a $N/10$ solution in carbon tetrachloride held at the boiling temperature for three hours only 24% of the thiocyanogen originally present remained unchanged. The loss, on exposure to light for the same period, was 10%. The solution remained practically unchanged in the dark.

Water causes the decomposition of thiocyanogen to thiocyanic, hydrocyanic and sulfuric acids, the reaction proceeding in stages as follows[236]:

$$NCS.SCN + H_2O \rightleftharpoons NCSOH + HSCN$$
$$2NCSOH \rightarrow HSCN + NCSO_2H$$
$$NCSOH + NCSO_2H \rightarrow HSCN + NCSO_3H$$
$$NCSO_3H + H_2O \rightarrow HCN + H_2SO_4$$

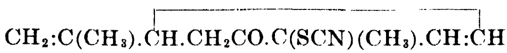
Ethylene reacting with thiocyanogen in direct sunlight gives *sym.* dithiocyanoethane, $NCS.CH_2CH_2SCN$; dithiocyanates are also obtained from styrolene and stilbene. Acetylene gives *trans*-dithiocyanoethylene which isomerizes in benzene solution under the influence of light. Bromine, reacting with *trans*-dithiocyanoethylene in the absence of a solvent, gives dibromodithiocyanoethane, NCS.CHBrCHBrSCN, m.p. 110°; when a solvent is employed, and the reaction is carried out in the light, the product consists of a mixture of tribromothiocyanoethane, $Br_2CHCHBrSCN$ and polymers of thiocyanogen. *Phenylacetylene* and *tolane* in benzene solution fix thiocyanogen in the dark giving phenylacetylene dithiocyanate, m.p. 67° and α-tolane dithiocyanate, m.p. 194° respectively[254].

Butadiene adds one molecule of thiocyanogen giving 2,4-dithiocyanobutene in 80% yield[263]. Isoprene and dimethylbutadiene give well-defined, crystalline dithiocyano compounds[264].

Thiocyanogen is capable of displacing bromine and iodine from organic compounds; thus reacting with dibromoethylene it gives thiocyanobromoethylene, dithiocyanoethylene, as well as tribromothiocyano- and dibromodithiocyanoethane, the last two forming as a result of the reaction of the bromine liberated with the ethylenic compounds present[254].

Addition fails to take place in particular cases; thus, ***styryl methyl ketone***, $C_6H_5CH{:}CHCO.CH_3$, forms a substitution product[218], $C_6H_5CH{:}C(SCN).$-

$COCH_3$. A monothiocyano substitution product,



$$CH_2{:}C(CH_3).CH.CH_2CO.C(SCN)(CH_3).CH{:}CH$$

is also obtained from carvone[219].

Substitution in the nucleus takes place also when thiocyanogen reacts with *aromatic amines*[220] and *phenols*[221]. *p*-Thiocyanoaniline, m.p. 57°, forms from aniline; dithiocyano compounds have been made from phenylenediamines. 1,2-Diamino-4,5-dithiocyanobenzene forms from *o*-phenylenediamine; the 1,3-diamino-4,6-dithiocyano-isomer forms from the *meta*-compound, and the 1,4-diamino-2,3-dithiocyano isomer from the *para*-compound[220]. The thiocyano-compounds made from phenols are converted to polyphenols by treatment with cold, 50% potassium hydroxide solution[221].

Thiocyanogen in solution in carbon tetrachloride reacts with *anhydrous ammonia* forming ammonium thiocyanate:

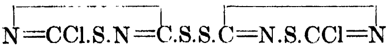
$$6(SCN)_2 + 8NH_3 \rightarrow 6NH_4SCN + N_2$$

At the same time much polymerized thiocyanogen forms[223]. Lecher and co-workers[236] obtained $NCSNH_2$ and hydrosulfocyanic acid, NCS.OH, by the reaction of ammonia and thiocyanogen. The amide explodes spontaneously above 0°. With aliphatic or substituted aliphatic *amines* thiocyanogen gives thiocyano-amines, the polymer of thiocyanogen forming simultaneously. Thus, thiocyanobenzylamine, $C_6H_5CH_2NHSCN$, and benzyl sulfocyanamine, $C_6H_5CH_2N(SCN)_2$,-m.p. 104°, result from the reaction of thiocyanogen with benzylamine. Diisoamylsulfocyanamine, $(C_5H_{11})_2NSCN$, m.p. 180°, and methylsulfocyanamine, $CH_3N(SCN)_2$, m.p. 102°, have also been made[220].

Reacting with hydrogen sulfide, thiocyanogen gives thiocyanosulfide[265] $S(SCN)_2$. Reaction with mercaptans RSH results in the formation of thiocyanosulfides[266] RSSCN.

Triphenylphosphine reacting with thiocyanogen yields triphenylphosphinesulfide; triphenylstilbine gives a dithiocyano compound[218].

Thiocyanogen reacts with hydrogen chloride in ether solution forming tetracyanodichloride, $(SCN)_4Cl_2$, which probably has the structure

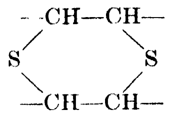


$$N{=}CCl.S.N{=}C.S.S.C{=}N.S.CCl{=}N$$

and another, unidentified compound[237].

Thiocyanogen chloride has been obtained in 95% yield through the interaction of chlorine and thiocyanogen at −50 to −60°. Molecular weight determinations have shown that the compound exists in the trimolecular form[267] $(SCN.Cl)_3$.

Organic thiocyanates treated with sodium hydroxide are normally converted to disulfides. Dithiocyanates obtained through the addition of dithiocyanogen at the double bond of unsaturated fatty acids, thus treated, first yield unsaturated thiocyanates, which then change on further reaction with sodium hydroxide, to stable sulfurated compounds. Kaufmann and co-workers, who studied this reaction, demonstrated the absence of the disulfide linkage in these compounds, and considered the products to be dithian derivatives, *i.e.*, compound containing the linkage



Upon treating the sodium salts of these compounds with iodine, *factice-like*, rubbery polymers were obtained[76].

REACTIONS OF *ISO*CYANIDES

*Iso*nitriles are hydrolyzed with dilute acids to an amine and formic acid:

$$RN{:}C + 2H_2O + HCl \rightarrow RNH_2.HCl + HCOOH$$

The reaction takes place readily in the cold, in the case of some *iso*nitriles, very rapidly. Hydrochloric acid combines with *iso*nitriles, forming unstable addition compounds, such as, $2CH_3NC.3HCl$, which, however, decompose rapidly in water, giving an amine hydrochloride and formic acid.

Partial hydrolysis may be brought about with glacial acetic acid giving formamides, $RNH.COH$. *Iso*nitriles act as dehydrating agents toward glacial acetic acid in this reaction, forming acetic anhydride. *Iso*nitriles are not affected by cold aqueous alkalies. On reduction they give rise to substituted methylamines, $RNHCH_3$, and on oxidation with mercuric oxide they are converted into *iso*cyanates.

p-Tolyl *iso*cyanide combines with sodium ethoxide and from the reaction product the compound, $CH_3C_6H_4N{:}CHOC_2H_5$, may be obtained by treatment with an acid. This is a yellow liquid boiling at 231–232° under 734 mm, and becoming solid at 8°.

Mesoxallyl *p*-toluidide, $(CH_3C_6H_4N{:}COH)_2CO$, m.p. 187°, has been obtained by the reaction of *carbon oxychloride* with *p*-tolyl *iso*cyanide. It combines with water forming a hydrate, $(CH_3C_6H_4N{:}COH)_2C(OH)_2$, m.p. 120–123°. The compounds, $CH_3C_6H_4N{:}C(OH).COC_6H_5$, m.p. 111–113°, and $CH_3C_6H_4N{:}C(OH).COCH_3$, m.p. 108°, have also been obtained from *p*-tolyl *iso*cyanide and benzoyl- and acetyl chlorides, respectively. *Formic acid* combines with *p*-tolyl *iso*cyanide, giving formo-*p*-toluide, m.p. 54°.

*Iso*cyanides add two atoms of *halogens*, X, forming $RNCX_2$. Bromine reacts vigorously with undiluted ethyl *iso*cyanide and a resinous product results. The dibromo compound, $C_2H_5NCBr_2$, m.p. 50–55°, has been obtained by the action of bromine on a dilute solution of ethyl *iso*cyanide in chloroform or pure anhydrous carbon disulfide. This is a highly reactive compound readily decomposed by water[224]. *Iso*cyanophenyl chloride, $C_6H_5NCCl_2$, has been prepared through the action of chlorine on phenyl *iso*cyanide in chloroform solution. This compound reacts with sodium ethoxide forming $C_6H_5N{:}C(Cl)OC_2H_5$. The corresponding methoxy and phenoxy compounds have also been made; the former boils at 215°, the latter melts at 43° and boils at 168° under 12 mm.

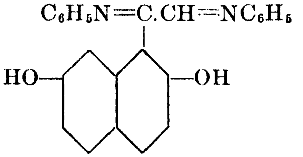
*Iso*cyanodichlorides reacting with amines give guanidines:

$$RN{:}CCl_2 + 4H_2NR' \rightarrow RN{:}C(NHR')_2 + 2H_2NR'.HCl$$

Dyson and Harrington[255] prepared the following guanidines by this method: Phenyldi-*p*-tolyl, m.p. 109°; phenyldi-m-tolyl, m.p. 93°; phenyldi-*o*-tolyl, m.p. 100°; phenyldi-*p*-bromophenyl (oil); *p*-tolyldiphenyl, m.p. 128°; tri-*p*-tolyl, m.p. 125°; *p*-tolyldi-*p*-bromophenyl, m.p. 178°; tri-*m*-tolyl, m.p. 107°; *m*-tolyldi-*p*-tolyl, m.p. 105°; tri-*o*-tolyl, m.p. 129°; *o*-tolyldi-*p*-tolyl, m.p. 87°; tri-*p*-bromophenyl, m.p. 126°; *p*-bromophenyldi-*p*-tolyl, 123°; *m*-nitrophenyldi-*p*-tolyl, m.p. 179°; *m*-nitrophenyldi-*m*-tolyl, m.p. 139°.

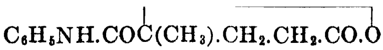
Elemental *sulfur*, heated at 120° with a carbon disulfide solution of *p*-tolyl *iso*cyanide forms *p*-tolyl *iso*thiocyanate, $CH_3C_6H_4NCS$. Heated with an alcoholic solution of *hydrogen sulfide* at 100° tolyl *iso*cyanide gives thioformo-*p*-toluide, $CH_3C_6H_4NH.CHS$, m.p. 175–176°. Under the same conditions ethyl *p*-tolyliminothioformate, $CH_3C_6H_4N:CHSC_2H_5$, forms with *ethyl mercaptan*. This is a yellowish liquid boiling at 250–252°; hydrochloric acid transforms it to di-*p*-tolylformamidine hydrochloride.

Phenol reacts in boiling alcoholic solution with phenyl *iso*nitrile to form the dianil of *o*-hydroxyphenylglyoxal[238], $C_6H_5.N{=}C(C_6H_4OH).CH{=}N.C_6H_5$, yellow crystals, melting at 151°; *β*-naphthol reacts similarly to form the dianil of 2-hydroxynaphthyl-1-glyoxal, colorless needles melting at 170°; *α-naphthol* gives the dianil of 6,7-benzocoumaronedione[239]. 2,7-Dihydroxynaphthalene gives the dianil of 2,7-dihydroxynaphthyl-1-glyoxal[238],



colorless needles melting at 175°. *β*-Naphthol reacts slowly with *p*-tolyl*iso*nitrile in benzene solution to form the ditoluidine derivative of 2-hydroxynaphthyl-1-glyoxal[240], almost colorless needles melting at 146–148°.

Phenyl*iso*nitrile and *salicylic acid* in *acetone* solution allowed to stand a week gives salicyl-*α*-hydroxy*iso*butyrylanilide, $C_6H_5NH.CO.C(CH_3)_2.O.CO.C_6H_4.OH$, colorless needles melting at 119°. Similarly phenyl*iso*nitrile, *benzoic acid* and *monochloroacetone* in ether solution give benzoyl-*α*-hydroxy-*β*-chloro*iso*butyrylanilide, $C_6H_5NH.CO.C(CH_3)(CH_2Cl).OCO.C_6H_5$, fine needles melting at 98°; under the same conditions acetyl-*α*-hydroxy-*β*-chloro*iso*butyrylanilide is formed with *acetic acid*. Similar compounds are obtained with methyl ethyl ketone, benzil, benzaldehyde piperonal and dichloroacetone[241]. The *iso*nitrile reacts slowly with *levulinic acid* in ether solution to form the lactone



$$C_6H_5NH.CO\overline{C(CH_3).CH_2.CH_2.CO.O}$$

which is decomposed with hydrochloric acid to aniline hydrochloride and the dibasic hydroxy acid[250] $HOCO.C(OH)(CH_3).CH_2.CH_2.COOH$. Propyl*iso*nitrile reacting in ethereal solution with *benzoic acid* and *benzaldehyde* gives benzoylphenylglycolylpropylamide, $C_3H_7.NHCO.CH(C_6H_5)OCOC_6H_5$, m.p. 118°; reacting with chloral hydrate it gives trichlorolactylpropylamide, $C_3H_7.NH.COCH$-

(OH).CCl$_3$, m.p. 117°. Hydrochloric acid decomposes the latter to trichlorolactic acid and propylamine[242].

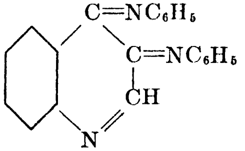
Hydroxylamine, reacting with phenyl*iso*nitrile in cold alcoholic solution forms phenyl*iso*urethine, $C_6H_5.NH.CH{=}NOH$, m.p. 138°; in acetone solution diphenylformamidine results[243].

Methylphenylpyrazolone reacts with phenyl*iso*nitrile to form the aniline derivative of 1-phenyl-3-methylpyrazolone-4-aldehyde,

$$C_6H_5N{=}CH.\dot{C}H.CO.N.(C_6H_5).N{=}\dot{C}.CH_3$$

yellow needles melting at 153–155°. Methenyl-bis-(1-phenyl-3-methyl-5-pyrazolone) results on boiling an aqueous solution of this compound[244]. *p*-Azobenzenephenyl*iso*nitrile heated to boiling with methylphenylpyrazolone gives the *p*-benzazoaniline derivative of methylphenylpyrazolone aldehyde. 1,3-*Diphenylpyrazolone* heated with phenyl*iso*nitrile gives methenyl-bis-diphenylpyrazolone, orange yellow needles melting at 250°; *1-methylpyrazolone* gives methenyl-bis-methylpyrazolone, yellow crystals which decompose at 315°[245].

Phenyl*iso*nitrile heated in benzene solution with *nitrosobenzene* forms a resinous mass from which two crystalline substances have been isolated. *Sym.*-diphenylurea and a compound of the empirical formula $C_{21}H_{15}N_3$ which is probably[246]



Heated in benzene solution with *α-nitroso-β-naphthol*, phenyl*iso*nitrile gives a black product which has not been identified. A complex reaction product is obtained under the same conditions with *p*-azobenzene*iso*nitrile and *α*-nitroso-*β*-naphthol and *β*-nitroso-*α*-naphthol[247]. Pernitrosocamphor allowed to react with phenyl*iso*nitrile for three weeks forms the anilide of *d*-bornylenecarboxylic acid[248].

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